

The
PROCEEDINGS
of

The American Association
for the Study and Control of
Rheumatic Diseases



FIRST ANNUAL MEETING AND THIRD
CONFERENCE HELD AT
Cleveland, June 11, 1934



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VICE-PRESIDENT.....DR. RUSSELL L. HADEN
SECRETARY.....DR. LORING T. SWAIM

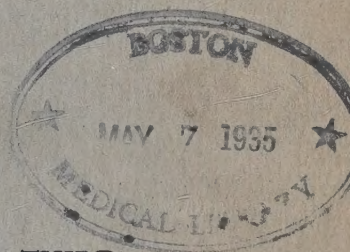
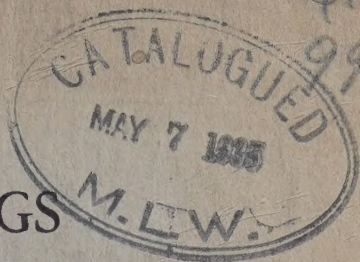


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THE NEW ASSOCIATION AND ITS PURPOSES: INTRODUCTORY REMARKS

ERNEST E. IRONS, M. D., PRESIDENT,
CHICAGO, ILLINOIS

May I express my thanks for the honor you have conferred in asking me to serve as the Chairman of this Association for the Study and Control of Rheumatic Diseases. The task is a pleasant one in that it offers opportunities for the renewal of contacts with old friends, and especially with the members of the American Committee whose labors of the past five years have done so much to forward knowledge of the important subject we are to consider.

PURPOSE OF THE ASSOCIATION

Almost every line of medical thought eventually begets a new society. It was the plethora of societies which made many of us hesitate when the formation of this association was first suggested. However, the need for extending the work so well begun by the American Committee, and the necessity for better correlation of what is known of arthritis, with what is done for the patient, convinced us of the desirability of this association. We hope that this organization will be not just another society, but rather an association of those interested in obtaining and promulgating a well rounded concept of the problem of arthritis, so that rational methods of treatment may be available to the physicians in charge of the many thousands of sufferers from arthritis, who must be cared for not only in larger medical centers but in smaller communities and in their homes.

MEMBERSHIP

It was deemed wise by the American Committee, who by the constitution of this association were made the Committee on Membership, that for the first year membership should be restricted to about one hundred, and should include in general those who have a deep and sincere interest in the study of rheumatic diseases and have made a definite contribution to its literature, or who hold positions of influence in the fields of public health and administration.

It is hoped that we may now extend membership, so that all parts of this country may be represented and the number of qualified participants in the work of the Association increased. Nominations for membership should be presented with proper credentials to Dr. Loring T. Swaim, Boston, the Secretary of the Association, for action by the Advisory Council.

Another activity of the Association will be the encouraging of the organization of local groups of those especially interested in the study of arthritis. Such groups will stimulate individual research, and promote general interest in the dissemination of knowledge of the disease and its treatment. In order that these purposes of the Association may best be carried out, and its discussions made accessible to as large a number of physicians

as possible, this meeting is for the present being held on the Monday preceding the Scientific Meeting of the American Medical Association. Here is afforded opportunity for the discussion of phases of arthritis in more detail than is possible in the larger meetings and at the same time close relation is maintained between this group and the scientific meetings of the American Medical Association.

It is unnecessary to review the work of the American Committee further than to outline the general problem. Chronic arthritis is the greatest single cause of disability and suffering in temperate climates.

A recent survey, 1933, of chronic disease in Massachusetts, showed that out of an estimated total of 500,000 sufferers from chronic disease, of whom 22,500 were totally disabled, there were 138,000 afflicted with rheumatism, of whom 5,600 were totally disabled. Heart disease, the leading cause of death, was next in frequency with 84,000 cases and 2,600 totally disabled. The magnitude of the suffering and disability caused by arthritis offers a major challenge to the medical profession and the public.

Many etiologic factors are operative in the early and later stages of chronic arthritis. These may include infections, trauma, exposure, heredity, malnutrition, inferiority of cartilage, and susceptibility to infection, glandular dyscrasias, dietary errors, gastro-intestinal dysfunction, and nervous and vascular disturbances which interfere with the nutrition of cartilage and bone. While one of these, such as chronic infection, may be the outstanding cause, the correction of which is sufficient to swing the balance toward recovery, it frequently happens that in spite of the correction of perhaps the initial cause, other factors continue to be operative and the arthritis progresses.

It is evident that a classification or a program of treatment of chronic arthritis based on the theory of one or another causative factor must fail in clinical use and that a broader view of the disease is required.

The division of chronic arthritis into two clinical groups, atrophic and hypertrophic, seems to the American Committee to offer the best clinical working classification for the present. The classification suggested by the British Committee in the excellent report of June, 1933,* is somewhat more detailed, but follows similar clinical lines. Both classifications recognize differences in age, course and morbid anatomy of the joints as well as differences in activity of demonstrable infections in the two groups. It is perhaps less important to know whether in the past infection may have been a predisposing or initiating cause in the patient with osteoarthritis, than to know that from experience with other similar cases the arthritis in this patient is less likely to progress to extreme crippling from ankylosis than is frequently the case in the atrophic group.

The conclusions reached through many of the studies on the relation of one cause, such as infection to chronic arthritis, have been invalidated by failure of observers to take into consideration the natural history of the disease. In chronic arthritis, especially in the atrophic type, periods of spontaneous improvement occur and conclusions as to etiology or therapy,

*Report of Committee on causation and treatment of arthritis and allied conditions. Brit. Med. Jour. 1:1033-1052 (June 17) 1933.

based on treatment instituted at the beginning of a period of natural improvement are likely to be misleading.

Chronic arthritis is to be thought of as a disease which affects the body as a whole, rather than the joints alone. For clinical purposes it may be divided into two types, the atrophic and the hypertrophic, although it must be admitted that these types may sometimes represent the outcome of perhaps similar series of events in different ages and types of persons in whom stimuli produce differing tissue reactions. Treatment must be highly individualized. Each patient presents a special problem, and the employment of one procedure for all patients in a disease whose etiology and course vary with each patient, seems unwarranted. While a spirit of optimism is desirable and necessary in this difficult field, it must still be recognized that in the present state of our knowledge there will be some patients whose disease is far advanced, and for whom but little can be accomplished. The number of these will be materially decreased as adequate broad-visioned treatment is instituted at an earlier stage before irreparable damage has been done.

The problem of arthritis is not static. Conceptions of its many angles alter slowly with advancing knowledge and experience. One of the chief functions of this Association is to furnish a forum in which, through discussion, new ideas may be evaluated and fitted in with what is already known.

Constructive criticism, kindly but frank, will be of great service in contributing to a safe but progressive program of treatment of arthritis. It is our hope that the work begun by the American Committee may be continued through the widened opportunities afforded by this Association.

THE ROLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN THE DEPOSITION OF COLLOIDAL AND PARTICULATE MATTER IN ARTICULAR CAVITIES.

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There are many phases in the physiological activity of joints which are still obscure. Many disturbances in functional activity, and pathological changes which come with disease, are understood even less well. While we have most careful studies of the end stage of many disease processes in joints, we have often little knowledge of what initiates the pathological changes, of their nature or in what manner they can be modified or arrested.

It is commonly believed that noxious substances which disturb articular physiology are carried to the joints by the blood stream. This is the usual path by which harmful material comes. Occasionally it may be introduced directly into the joint cavity from the outside or under unusual circumstances lymph flow may be retrograde in direction. But for the most part the substances animate or inanimate to which articular tissue reacts are brought by the blood stream.

Suppurative arthritis and tuberculosis of joints are regarded in practically all instances as the result of a hematogenous infection. A bacteriemia with subsequent lodgement of bacteria in capillaries, in or about the joints are supposedly the origin of such diseases. To what extent implanted bacteria can be encouraged or hindered in their growth by trauma or other mechanical or chemical factors is not fully known. In chronic arthritis also, we postulate the passage of bacteria or of poisonous substances to the joints usually from some foci of infection or from the gastrointestinal tract. Little interest had been shown as to how these substances entered the blood stream or were in turn removed from it.

There is in the human body a host of cellular constituents, distributed in the loose connective tissue, lining the sinusoids in the liver, spleen, and lymph nodes; forming a part of the reticulum of the spleen and of the bone-marrow which can be mobilized as a defense mechanism whenever unusual substances or bacteria are introduced into the body. Certain of these cells are constantly active under conditions of health in removing dead tissue or metabolic products by phagocytosis, transporting the material through the blood stream and storing it in such places as in the liver. From the places of storage these substances are slowly eliminated, usually by the intestinal tract. This group of cellular elements characterized by the common functions of phagocytosis and storage of materials greater than molecular size, particularly those of electro-negative potential, and by vital staining with certain acid dyes has been called by Laudau and Aschoff, the reticulo-endothelial system.

This system has widely divergent functions in the body. Probably its most important function is that of active phagocytosis as shown in inflammatory and reparative processes. Colloidal particles are engulfed and accumulated in granule like masses in vacuoles within the cell body. Bacteria or other substances may be stored in these cells presumably without disturbing the activity of the cell. Violent poisons or virulent bacteria, however, soon destroy the cells into which they are taken. It is thought that when the cells of the reticulo-endothelial system are unable to free the body from invading micro-organisms, that infection takes place and, likewise, that local injury of tissue results when toxic substances or bacteria cannot be removed with sufficient rapidity. Among the other functions of the reticulo-endothelial system are participation in general metabolic functions, the storage of fat and to a certain extent the production and storage of antibodies and immune substances.

While the numerous investigators have made no mention of articular tissues, it was supposed that this system played some part in articular inflammation and repair. This study was undertaken to ascertain the activities of this system in and about joints. Trypan blue in a 1 per cent aqueous solution was used for injection in most of the experiments. The young albino rat was chosen as the experimental animal since it is a very satisfactory animal for most studies of the reticulo-endothelial system. Observations were made of the nature and extent of the deposition of colloidal and particulate matter in and about the joints. Further studies were made to determine how this deposition could be modified by trauma, irritation, or attempted local blocking of the reticulo-endothelial system. Finally the deposition of material in articular cavities after absorption from the gastro-intestinal tract was studied. It was hoped that some relationship might be established between these findings and the problems of articular infection, and of disturbances in joints associated with systemic disease such as chronic arthritis.

EXPERIMENTS

Experiment 1.—Four rats were given subcutaneous injections of 2 c.c. of a 1 per cent solution of trypan blue every two days. The injections were made into the abdominal wall and the area was massaged gently to insure more complete absorption. This procedure was carried out under light ether anesthesia. The four animals were given 10, 11, 13, and 16 injections respectively. Death of some animals prevented an equal number of injections in each. Usually after several injections the animals became a dusky blue color. With long continuation of the injections the animals began to lose weight; they ate less well and became less active; the hair became rough, and was gradually lost. At this stage they would die without apparent cause.

At autopsy there was found extensive staining of the entire skin and subcutaneous tissue, besides the liver, spleen, kidney, and bone marrow. The joints showed a moderate amount of staining. Both femoro-tibial and humero-ulnar joints were removed for microscopical study. These were decalcified carefully in a 5 per cent aqueous solution of trichloroacetic acid in order to avoid solution of the stored dye. Most sections were stained

with paracarmine and a few with hematoxylin and eosin. The amount of dye found was roughly proportionate to the number of injections given. Single injections or a few injections in preliminary studies had shown practically no dye in the articular cavities. Numerous dye-laden histiocytes were seen in all portions of the joint just beneath the epithelial-like layer of the synovial membrane.

A study was made of the absorption of a mixture of dyes, the particles of which varied from the ultra-microscopic (trypan blue), through particles barely visible by the microscope (sodium carminate) to particles readily seen by the lower microscopical magnifications (India ink). A mixture of equal parts of a 1 per cent solution of trypan blue, a 1 per cent solution of sodium carminate and a 50 per cent suspension of filtered India ink was injected in doses of 2 c.c. subcutaneously into two rats biweekly for 7 and 11 times respectively. The mixture was absorbed much more slowly than trypan blue alone. After a few injections there was necrosis of the skin at the site of injection. The animals died after the number of injections previously mentioned had been given. Because of the marked irritation of this mixture no further studies were made.

Microscopical study of the joints of these animals showed less deposition of trypan blue in the synovial membrane, chiefly in histiocytes. There was only a small amount of sodium carminate scattered about in histiocytes. No India ink was found in the synovial membrane. As no extended study was made no definite conclusions can be drawn, but the histological findings suggest lessened absorption and deposition of particulate matter in proportion to the size of the individual precipitated particles.

The dye was found less abundantly in the deeper layers of the synovial membrane. There was a moderate amount scattered throughout the reticulum of the bone marrow. The fat pad in the knee-joint was almost entirely devoid of dye-laden phagocytes. The dye was found chiefly in histiocytes which could be differentiated readily by the nuclear and cytoplasmic character from fibrocytes. The trypan blue was deposited in granule-like clumps in vacuoles in the cytoplasm. Scattered fibrocytes were seen somewhat deeper in the synovial membrane containing some trypan blue deposited in their cytoplasm in the form of fine granules or short rods. In the bone marrow the trypan blue was wholly in the histiocytes of the reticulum. None was seen in either bone or cartilage cells. In this group of animals there was observed a slight increase in the fibrous tissue but there was very little evidence of an inflammatory response within the joint itself. There seemed to be a slight increase in the number of blood capillaries seen. There were individual variations in the amount of trypan blue found in the joints as might be expected. The animal that had received sixteen injections showed the largest amount of dye deposited in the synovial membrane. Here there was a dense layer of dye-laden histiocytes beneath the epithelial-like layer of the synovial membrane. In a few places the surface epithelium was lost and the histiocytes were arranged on the surface-like cuboidal epithelium.

This group of animals, besides preliminary studies, showed that material larger than molecular size could be carried from the skin and subcutaneous tissues and stored in the joints. Most of this material was carried probably by the mobile cells of the reticulo-endothelial system; some was transported probably in solution or suspension by the tissue fluids to the blood or lymphatic stream. M. R. Lewis has shown that solutions of trypan blue are precipitated in the blood stream and the particles are taken up by the cells of the reticulo-endothelial system. All available evidence suggests that bacteria, metabolic products not in solution, and tissue debris are handled in a similar manner.

Experiment 2.—Four rats were given 11, 13, 19, and 23 injections respectively of 2 c.c. of a 1 per cent solution of trypan blue subcutaneously every two days. At the same time 0.1 c.c. of a 20 per cent solution of potassium iodide was injected into the right humero-ulnar and femoro-tibial joints.

In this group of animals the findings in the left joints were similar to those described in Experiment 1. The animals that had received 19 and 23 injections of trypan blue showed much more dye than those of the previous series. The histiocytes were much enlarged. The cytoplasm was so crowded with granules of trypan blue that the individual vacuoles were often invisible. Some cells were almost black. The cell shape was altered because of the large number and crowding of the cells. The fibrocytes contained an unusually large amount of the dye in granules and short rods. There was a slight increase in the synovial connective tissue. Considerable dye was seen in the bone marrow. Numerous histiocytes were scattered among the fat cells of the articular fat pad and in the fatty marrow. Many dye-laden histiocytes were seen in the intermuscular septa. Less trypan blue was found in the humero-ulnar joints in all of these cases than in the femoro-tibial joints.

In contrast, the joints on the right side, into which had been injected a 20 per cent solution of potassium iodide in order to produce a mild aseptic, inflammatory reaction, showed considerably more deposition of the trypan blue than the joints on the left side. The histiocytes were so full of the dye in many instances that the cytoplasm was completely obscured. The joints showed rather extensive proliferation of the synovial membrane with a great increase of the folds or villi and it was in these folds that the largest amount of trypan blue was found. In a number of places the epithelial-like layer was much thickened, in others, it had disappeared entirely and histiocytes full of trypan blue were seen in parallel layers almost like epithelium. There was a great increase in fibrocytes, and the blood vessels appeared to be engorged considerably. No evidence of thromboses of any vessels was seen.

The findings in these animals suggested that a local inflammatory response caused a greater deposition of trypan blue. It is impossible, however, to measure the amount of dye present in a joint. Whether this apparent increase in trypan blue in the joints, into which repeated injections of potassium iodide had been made, was the result of an increased local proliferation of histiocytes or an increased migration from without

could not be determined. Occasional mitotic figures were seen in histiocytes. Fibrocytes in synovial membranes rarely show mitoses. Previous observers have seen increased deposition of substances in tissues in inflammation. Studies by Böhm, and others, suggest that a mild inflammation stimulates the activity of the reticulo-endothelial system, while a severe inflammatory response hinders it.

Experiment 3.—In a series of four rats a blow was struck directly upon the right femoro-tibial joint, sufficient to produce swelling for several days. This was repeated twice weekly, and at the same time subcutaneous injections of 2 c.c. of a 1 per cent aqueous solution of trypan blue were made. The animals received 6, 11, 13, and 21 injections respectively. At autopsy both humero-ulnar and femoro-tibial joints were removed.

The microscopical picture was similar to that described before. The amount of distribution of trypan blue was about equal to that seen with a like number of injections in the previous series. In the joints on the right side so far as could be determined there was little, if any, increase in the amount of trypan blue. There was a rather marked increase in the connective tissue. No increase or apparent dilatation of the blood vessels was observed. The fibrocytes tended to assume layer-like formations parallel to the synovial surface. Many young fibrocytes were seen and cells which suggested transitional forms. As in previous sections there was a tendency on the part of the histiocytes to approach the surface and form an epithelial-like layer. Dye-laden histiocytes were seen in tags of synovial membrane and they gradually decreased in number as the membrane approached the hyaline cartilage of the joint.

In the traumatized joints there seemed to be a much greater accumulation of dye-laden histiocytes in the periarticular tissues. Perhaps with more severe mechanical trauma there would have been sufficient inflammation to cause an increase, also, in the histiocytes in the synovial membrane.

Experiment 4.—In an attempt to produce a local blocking of the reticulo-endothelial system, repeated injections of India ink were given into the right femoro-tibial and humero-ulnar joints. Ten injections of 0.1 c.c. were given twice a week to four animals. Subsequently, bi-weekly injections of 2 c.c. of a 1 per cent solution of trypan blue were given subcutaneously for 2, 11, 13, and 14 times respectively.

Microscopical study showed many carbon particles on the surface of the synovial membrane, some enmeshed in fibrin, on the right side. Many superficial histiocytes were seen containing a large amount of India ink. Very little ink was seen in fibrocytes. A little trypan blue appeared in histiocytes, but for the most part this was masked by the large amount of India ink. There was a moderate proliferation of the synovial membrane. In one section there were a number of histiocytes and round cells engorged with India ink in a lymphoid-like mass in the bone marrow, showing apparently an unusual collateral lymphatic circulation in this instance. The findings on the whole were disappointing; the amount of India ink masked the histiocytes so completely that the trypan blue could not be seen, and no definite conclusion could be drawn as to the local

ability of the tissue to pick up and store the dye. The microscopical sections from the joints on the left side where no India ink had been injected showed the usual amount and location of the trypan blue. Injections of India ink intra-articularly and trypan blue subcutaneously at the same time for repeated injections in several rats gave the same inconclusive findings. Other investigators have shown that it was impossible to fill the cells of the reticulo-endothelial system so completely that no further material could be phagocytosed, but a stage of lessened activity is reached temporarily. Such depression of phagocytic activity, the so-called endothelial blockade, is temporary and the material unless entirely inert or extremely irritating is soon removed from the body.

Experiment 5.—A further attempt was made to block the reticulo-endothelial system by the intra-articular injections of oil. Twelve injections of 0.1 c.c. mineral oil colored with Sharlach R, were made into the left femoro-tibial joint of six rats at biweekly intervals. Injections of 2 c.c. of a 1 per cent solution of trypan blue were then given subcutaneously biweekly for 10, 11, 11, 12, 15, and 18 times respectively. At autopsy both humero-ulnar and femoro-tibial joints were removed.

Pinkerton in his studies of the reaction of the bronchioles and alveoli to injected oils found that there was a less vigorous inflammatory response to a hydrocarbon such as mineral oil. In this group of animals the humero-ulnar and the right femoro-tibial joints displayed trypan blue in the synovial membrane much like that shown in the previous experiments. In the left femoro-tibial joints there was moderate synovial proliferation. Small amounts of oil were observed within the joint cavity. A small amount was present in tiny globules in histiocytes, superficially in the synovial membrane. The amount of trypan blue present in the synovial membrane was apparently equal on the two sides.

This experiment suggested that a definite local blocking of the reticulo-endothelial system to the deposition of trypan blue could not be produced by an organic oil of low toxicity such as liquid petrolatum. Organic oils, like olive oil were used for injection extensively a decade ago by Baer and others in the mobilization of stiffened joints, but their use was discontinued because fibrosis and increased stiffening of the joints resulted. Mineral oil is absorbed slowly when injected into tissues as numerous observers have found, but the rate and amount of absorption is not sufficient to produce a noticeable local change in the function of the reticulo-endothelial system.

Experiment 6.—In two rats 8 c.c. of a 2 per cent solution of trypan blue was given by stomach tube intra-gastrically twice weekly for seven and fourteen times respectively. The injections were apparently well tolerated; the animals seemed to remain in good health and ate heartily. There was slight blue staining of the feces. The animals slowly became blue in color but the staining of the skin was much less than in any of the animals receiving an equal number of subcutaneous injections.

At autopsy there was marked staining of the lower end of the esophagus and the stomach with less staining of the intestinal tract which faded out entirely when the transverse colon was reached. The mesenteric lymph

nodes were stained a deep blue. There was a moderate amount of blue staining of the diaphragm, liver, spleen, and kidneys. The femoro-tibial joints showed a moderate deposition of trypan blue in histiocytes chiefly, similar in location to that seen in previous studies. In no case was this equal to the amount observed after subcutaneous injections.

This study showed that articular absorption could result by way of the reticulo-endothelial system from the gastro-intestinal tract. Apparently a longer time is required and greater amounts are necessary, at least, to produce a demonstrable deposition in synovial membrane. It is well known that trypan blue given orally is not absorbed readily at first, but later after considerable damage has been done to the mucosa of the gastro-intestinal tract, marked absorption takes place. Clinically, we have proof of the close relationship between purin metabolism and the deposition of urates about articular cavities. Evidence has been offered by Fletcher, Osgood, and others of the appearance of joint disturbances in faulty intestinal elimination. The joints of these experimental animals showed how readily material from the gastro-intestinal tract could be taken up either primarily by the reticulo-endothelial system or after absorption from the gastro-intestinal tract and deposited in the synovial tissues.

The reticulo-endothelial system in its relation to joints becomes of more than academic importance when we consider not only that materials greater than molecular size are carried to articular cavities from tissues and the gastro-intestinal tract but also that materials given by intravenous injection in the treatment of arthritis which do not remain in solution are removed from the tissues or the circulating blood by this aggregation of phagocytic cells of the reticulo-endothelial system. Any part which they play in the articular cavities is through the mediation of this system. In observing the inequable distribution and the feebler phagocytosis and storage in joints in comparison with other tissues, one wonders how effective the solutions of intricate molecular composition and the host of colloidal solutions are as bactericidal agents or metabolic stimulants.

In any study of the function of the reticulo-endothelial system due consideration must be given to the liver. This organ probably plays the part of intermediary in all toxic substances absorbed from the gastro-intestinal tract. Whether toxic substances only reach joints when they are brought in too large quantities or when the functional activity of the liver is impaired, we do not know. Substances and bacteria absorbed from the skin or superficial tissues in many instances can reach joints without passing through the liver. The same is probably true of bacteria or harmful substances coming from foci of infection. This study shows the common mechanism of the manner in which substances can be removed from tissues of the body and the gastro-intestinal tract and can be stored in articular membranes. All the evidence suggests that bacteria and toxins not in solution are removed in the same manner.

The most important question, and one unanswerable in the present state of our knowledge is: How can we use the function through mechanical or pharmacological stimulation in the therapy of articular diseases?

The reticulo-endothelial system plays a rôle in the absorption of injected substances such as vaccines, but we do not know whether the final action is humoral or through the cells. Apparently changes in sensitivity and anaphylaxis are the result of change in the capacity of the cells of the reticulo-endothelial system to respond to certain chemical substances.

CONCLUSIONS

1. Colloidal and particulate matter is carried to articular cavities from body tissues and the gastro-intestinal tract through the action of the cells of the reticulo-endothelial system.

2. Such transported substances are stored chiefly in histiocytes in the villi just beneath the epithelial-like layer of the synovial membrane. Large amounts are stored in the bone marrow. Less amounts are seen in the inter-muscular septa and in the articular fat pad.

3. Mild inflammation in articular tissues tends to increase the amount of deposition of such injected substances.

4. Local blocking of the reticulo-endothelial system apparently is transitory and is ineffective in preventing the deposition of colloidal and particulate matter injected elsewhere.

DISCUSSION

DR. ROBERT B. OSGOOD, Boston: Dr. Kuhns and Dr. Weatherford seem to have proved that materials of greater than molecular size can be carried to the joints from the gastro-intestinal tract and from other tissues by the medium of the agents belonging to the reticulo-endothelial system. This is knowledge in place of assumption. However, such possible etiologic material seems to be stored in the articulations less easily than in other tissues, e.g., the bone marrow. The corollary of this knowledge suggests the question which the investigators very sanely raise as to whether various injected substances, vaccines, etc., are likely to be very effective therapeutically in arthritis, considering their intricate molecular composition and the many colloidal solutions which would seem to be probably much attenuated and perhaps actually changed in composition before they can reach the joint tissues. The paper is so thought provoking that it stimulates the hope that its authors will continue their research along these lines.

DR. JOSEPH KOVACS, New York: I hardly believe that acute inflammations in general stimulate the cells of the reticulo-endothelial system to increased activity. Under such conditions an increase in deposits of dye might be explained by the fact that in acute inflammation there is an increased supply and perhaps stasis of blood which would enable the histiocytes to absorb and store more dye from the blood. Although an impaired circulation can be found in over half of the cases of chronic arthritis, I doubt that an increased dye storage could be found except in the more acute or subacute stages where increased blood supply and stasis are present.

CALCIUM AND CHOLESTEROL METABOLISM IN ARTHRITIS*

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Rheumatoid and osteo-arthritis are now accepted as general constitutional diseases. There is no doubt, however, that their grosser manifestations are seen in the bones and related structures. This observation directs attention to the metabolism of the mineral constituents of bone. The most important of these is calcium. There are two methods of approach to the study of this element—by calcium balance experiments and by determinations of the blood serum calcium.

Calcium balance experiments in arthritis have been few and are inconclusive. Published reports on the blood serum calcium are also few and still more conflicting. The most extensive studies were those of Pemberton and Foster, Cajori and Crouter who found that the serum and plasma calcium were within the limits usually ascribed to normal blood. The object of our study was to review this question, at the same time differentiating the cases into the two accepted groups, rheumatoid arthritis and osteo-arthritis.

METHOD

We took in sequence 50 cases of rheumatoid arthritis and 50 cases of osteo-arthritis, and determined the blood serum calcium in each. The cases came from one clinic and the determinations were all done in one laboratory. Clark's modification of the Kramer and Tisdall method was used throughout.

The results of these determinations are compared with 852 control cases, all done at The Mayo Clinic by a method identical with our own. These figures are from unpublished compilations of Carl H. Greene and Philip S. Hench. In addition our results are compared with 128 controls from our own hospital laboratory.

SUMMARY OF RESULTS

Table 1 represents a summary of these determinations, together with their statistical analysis. The arithmetic mean of the calcium determinations in the 50 rheumatoid-arthritis cases is 10.27 mg. per 100 c.c., almost identical with the mean of the two control groups. The mean of the 50 osteo-arthritis cases is 10.04. That this mean shows a significant deviation from the mean of the control group A is indicated by the magnitude of the result when the difference between these two means is divided by the standard error of the difference between these means. The same result is obtained using control group B as a standard.

*From the Department of Medicine, New York Post Graduate Hospital.

DISCUSSION OF RESULTS

There is, therefore, a slight but definite decrease in the amount of calcium in the blood of osteo-arthritis patients. This decrease may be due to a primary disturbance in calcium metabolism or may be due to one or more secondary associated factors characteristic of the osteo-arthritis group. Further study would be necessary to determine the true cause.

Table 1
Serum Calcium in Arthritis

	Number of Observations	Arithmetic mean (mg. per 100 c.c.)	Standard Deviation	Probable error of mean	$\frac{d}{6 \text{ D}}$
Controls A Mayo Clinic	852	10.291	0.647	0.015	— — —
Controls B. N. Y. P. G. H.	128	10.281	0.777	0.046	— — —
Rheumatoid Arthritis	50	10.272	0.701	0.067	0
Osteo-arthritis	50	10.044	0.625	0.060	2.71

Table 2
*Serum calcium in hypertension, arteriosclerosis, endarteritis obliterans
and osteo-arthritis.*

	Number of Observations	Arithmetic mean (mg. per 100 c.c.)	Standard Deviation	Probable error of mean	$\frac{d}{6 \text{ D}}$
Hypertension and Arteriosclerosis*	34	10.265	0.710	0.082	0.3
Endarteritis Obliterans*	57	10.317	0.763	0.068	0.4
Osteo-arthritis	50	10.044	0.625	0.060	2.71

*From unpublished compilations of Carl H. Greene and Philip S. Hench.

Table 3
Plasma Cholesterol in Arthritis

	Number of Observations	Arithmetic mean (mg. per 100 c.c.)	Standard Deviation	Probable error of mean	$\frac{d}{6 \text{ D}}$
Controls	33	194.66	29.32	3.42	0
Rheumatoid Arthritis	33	175.20	39.50	4.60	2.27
Osteo-arthritis	59	235.42	45.09	3.69	5.20

Among the associated factors one might mention age, for osteo-arthritis are usually advanced in years. The average age of our osteo-arthritic group was 52 years, compared with 40 for the rheumatoid group. That

age is not the determining factor, however, is suggested by table 2 which compares our figures with Dr. Greene's compilations on groups of patients with hypertension and arteriosclerosis, and with endarteritis obliterans. Both these groups are comparable in age to our own osteo-arthritis group. The calcium determinations however are not low, but approximate normal.



Fig. 1

Frequency distribution of plasma cholesterol, mgms. per 100 c.c. in normal, osteo-arthritic and rheumatoid arthritic subjects.

Changes in the plasma proteins, and anemia may play a part. Hypochlorhydria, more common with advancing years, may be a factor. Defective intestinal absorption of calcium is a suggestive explanation. With ad-

vancing years, intestinal putrefaction is more common, and this is associated with a relatively more alkaline intestinal content which, as has been shown, decreases the absorption of calcium.

CHOLESTEROL METABOLISM

It has been observed that there is a significant decrease in the blood plasma cholesterol in some infections. Bruger and Poindexter at the New York Post Graduate Hospital found an elevation in a few cases of osteo-arthritis. Pemberton and Foster in 1920 did suggestive work on blood cholesterol. We wished to review this study, separating the cases into the two recognized groups, rheumatoid and osteo-arthritis.

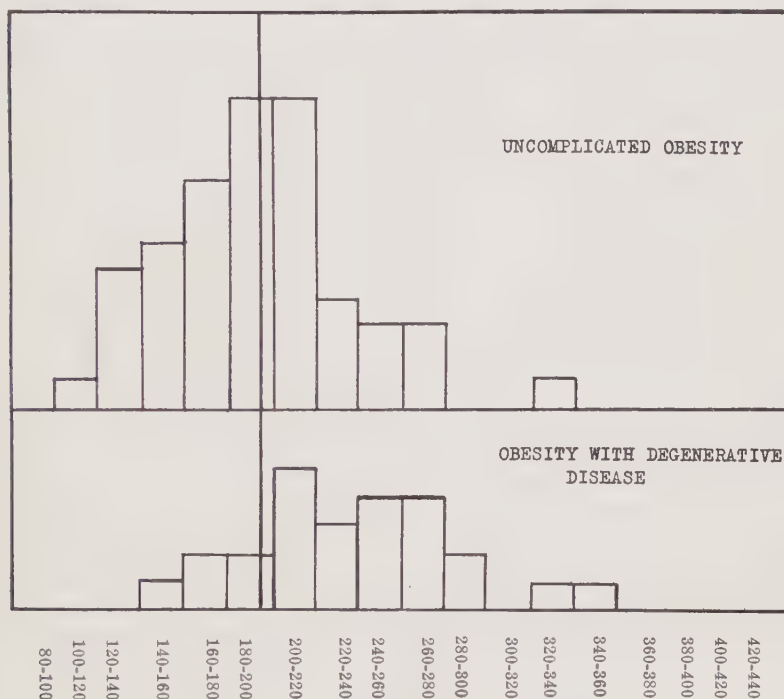


Fig. 2

Frequency distribution of plasma cholesterol mgms. per 100 c.c. in uncomplicated obesity and obesity with degenerative disease. (Bruger and Poindexter).

METHOD

At present we have made determinations on 59 cases of osteo-arthritis and 33 of rheumatoid arthritis. The cases were personally selected. All the clinical criteria at present available were used to differentiate the two types. The method used was that of Sackett (Modified Bloor Method).

SUMMARY OF RESULTS

Table 3 and figure 1 represent a summary of these determinations together with the determinations on 33 normal subjects. The arithmetic mean for the osteo-arthritis group was 235.4 mg. per 100 c.c., and for the rheumatoid group 175.2, compared with 194.6 for the control group. Statistical analysis as described in the summary on calcium above shows that

there is a significant elevation of cholesterol in osteo-arthritis and a suggestive but not definite decrease in rheumatoid arthritis.

DISCUSSION OF RESULTS

An elevation of the plasma cholesterol in osteo-arthritis suggests that osteo-arthritis is a degenerative disease. Similar elevations are found in other degenerative diseases such as essential hypertension, arterio-sclerosis, and in diabetes. Thus Maurice Bruger (fig. 2) found that in uncomplicated obesity there was no variation from normal, whereas in obesity associated with degenerative disease there was a significant elevation. The elevation found by us in osteo-arthritis cannot, therefore, be explained on the basis of obesity.

The suggestive decrease of cholesterol in rheumatoid arthritis is compatible with the usually accepted infectious etiology of the disease. Some of our lowest determinations for cholesterol (not reported here) were found in acute rheumatic fever. In one of these cases the cholesterol was 89.5 mg. per 100 c.c.

CONCLUSIONS

1. There is a slight but significant decrease of the serum calcium in osteo-arthritis. This decrease cannot be explained by the fact that this disorder occurs in an older age group.

2. The serum calcium in rheumatoid arthritis does not show a significant variation from normal.

3. There is an increase of plasma cholesterol in osteo-arthritis. This increase cannot be explained by the fact that patients with this disorder tend to be obese.

4. The plasma cholesterol in rheumatoid arthritis tends to be lower than the average normal.

A STUDY OF THE ROENTGENOLOGIC FINDINGS IN VARIOUS TYPES OF CHRONIC ARTHRITIS*

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During the past two years at the Arthritis Clinic of the Presbyterian Hospital and the X-ray department of the New York Orthopedic Dispensary and Hospital we have been engaged in an extensive study of the roentgenologic findings in various forms of chronic arthritis. The present paper is submitted as a preliminary report on one phase of that study.

From a total of 300 patients examined in detail, a representative number of each of the more common forms of the disease was selected. These patients were selected because they presented only the characteristic clinical and laboratory findings of the type of arthritis they represented. The groups chosen were as follows:

- I. Rheumatoid arthritis, 52 cases.
- II. Osteo-arthritis, 32 cases.
- III. Gout, 12 cases.
- IV. Gonococcal arthritis, 11 cases.
- V. Tuberculous arthritis, 32 cases.
- VI. Marie-Strümpel Spondylitis, 12 cases.
- VII. Still's disease, 12 cases.

The diagnostic criteria for classifying the chronic non-specific arthritides, viz., rheumatoid (atrophic) and osteo-(hypertrophic) arthritis are those outlined by Dawson, Sia and Boots, Cecil and others.

I. The typical *rheumatoid arthritis* patients averaged 49 years of age, with an average 5 year duration of symptoms which were classical of the disease. (1) The majority showed typical fusiform swelling or contracture deformities, and many had subcutaneous nodules. (2). They were the apparent victims of a chronic infectious process and malnutrition; and they ran a consistently high erythrocyte sedimentation rate, averaging 50 mm. per hour. (3). The majority, 43 patients, gave positive serum agglutination to the hemolytic streptococci in high dilutions; (4) of the remaining 9 patients, 2 were negative, and 7 were not recorded.

(Ages, 22-72 years; duration, 2 months—18 years; Sedimentation Rate, 3-118 mm. per hour.)

II. The *osteo-arthritis* patients averaged 53 years of age, and had a history of average duration of 6 years. The majority were overweight, had comparatively mild symptoms, and the larger weight-bearing joints were chiefly involved. Many had Heberden's nodes. There was little evidence of infection; the erythrocyte sedimentation rate averaged 19 mm. per

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University, the Arthritis Clinic of the Presbyterian Hospital, and the New York Orthopedic Dispensary and Hospital, New York City. The Arthritis Clinic of the Presbyterian Hospital is supported by the Faulkner Memorial Fund.

hour, and there were no definitely positive hemolytic streptococcus agglutinations, although 8 patients did show a questionable trace.

(Ages, 32-65 years; duration, 1-36 years; Sedimentation Rate, 4-54 mm. per hour.)

III. The *gout* patients averaged 54 years of age, and gave a history of recurrent painful attacks in one or more of the small joints. Several showed tophi, and all had high blood uric acid values, averaging 6.1 mgm. per cent, without apparent renal damage.

(Ages, 34-74 years; blood uric acid, 3.5-9.6 mgm. per cent.)

IV. The patients with *gonococcal arthritis* were otherwise healthy; the average age was 27 years; the average duration 10 weeks. All but one had mono-articular involvement, and all had recent urogenital infections. In 73 per cent (8 patients) of the group, the specific Neisserian organism or a positive gonococcus complement fixation test was obtained to substantiate the diagnosis.

(Ages, 20-36 years; duration 4-36 weeks.)

V. The *tuberculous arthritis* patients varied in age from 7 months to 67 years. The slowly progressive symptoms lasted for an average of 6 years and all except 3 of the 32 cases were mono-articular. The diagnosis was verified subsequently in most of the cases by guinea-pig inoculation or by histological sections obtained at the twenty fusion and two drainage operations.

(Ages, children average 5 years, adults average 35 years; duration 1 month—46 years.)

VI. The 12 *Marie-Strümpell arthritis* patients, average age 33 years, showed a definite ankylosing type of spondylitis with a tendency to round-back deformities. Although the average duration was 7 years, only one patient had symptoms in the extremities. There was only one positive agglutination to hemolytic streptococci, although 6 were reported "doubtful," but the average erythrocyte sedimentation rate was 49 mm. per hour.

(Ages, 21-52 years; duration, 2-12 years; Sedimentation Rate, 30-79 mm. per hour.)

VII. The eleven children with *Still's disease*, age 1 to 10 years at onset gave an average 21 months' history of polyarthritis of the smaller joints, with characteristic fusiform swelling of the fingers, and all had evidence of various chronic local infections. As expected in this age group, agglutination to the hemolytic streptococci was essentially negative although one patient did give a positive reaction (1.160) and 4 were reported "doubtful," but the consistently high erythrocyte sedimentation rate averaged 51 mm. per hour.

(Average age at onset, 4 years; Sedimentation Rate, 4-127 mm. per hour.)

During this study, the roentgenologists were given no clinical information concerning the patients except the *duration* and *severity* of the symptoms (i.e., regarding the degree of function or immobility). Their findings were recorded separately on a chart form listing 15 chief items with 49 detailed descriptive roentgenologic subdivisions. Six of the more out-

standing items are presented in this preliminary report, and may be defined as follows:

1. (a) *General decalcification* is a decrease in bone density, not limited to a small area, but includes all the bones shown on any one film. It is often termed "osteoporosis." If generalized throughout the bony skeleton the decalcification is then said to be "systemic," e.g., that which occurs to a slight degree normally in middle and old age.

(b) *Local decalcification* is a decrease in bone density in a circumscribed area, e.g., near one joint only.

2. *Bone production.* (a) *Lipping* is a calcareous deposit at the joint margin. It is small, pointed, and tends to conform to the adjacent soft tissues.

(b) *Osteophytes* are larger desposits, more irregular and exuberant, and often occur in ligamentous structures.

3. *Loss of bone substance* is a localized loss of calcium and bone architecture. Two varieties are recognized and require further definitions:

(a) *Active* loss of substance shows the surface of the remaining bone spiculated and eroded; the calcium density is decreased in the surrounding area, and in subsequent examinations the process tends to show progression.

(b) *Atrophic* loss of substance can be recognized only at the bone margin, usually at or near the joint. It consists of smaller or larger areas that are smooth, sharp, and "punched out" in appearance. These areas stand out in sharp contrast to the soft tissues, and there is *no* decrease in the calcium density of the surrounding bone. (These "punched-out" areas were formerly ascribed chiefly to gout.)

4. *Joint space* is narrowed or obliterated (or even widened) according to the degree of destruction of the articular cartilage which this "space" represents on the films.

5. *Ankylosis* occurs at the site of destroyed cartilage.

(a) *Bony* ankylosis shows continuous bone trabeculae from bone end to bone end. It may occur in joints that are essentially immovable (e.g. sacro-iliac) or in other joints that have had previous cartilage damage.

(b) *Fibrous* ankylosis can only be estimated from the roentgenograms. It is evidenced by failure to show a joint space in the absence of bony ankylosis.

6. *Soft tissue changes.*

(a) *Atrophy* is indicated by a decrease in the diameter of the soft tissues. (Hence the necessity for a contrast film of the other corresponding extremity is obvious.)

(b) *Swelling* is indicated by an increase in the diameter of the soft tissues outside the capsule.

(c) *Effusion* is indicated by an increase in the diameter of the soft tissue shadow represented by the capsule and its contents. The capsule is usually outlined by the adjacent fat pad. The effusion is described further as being:

- i dense or not dense, according to the intensity of shadow.
- ii sharp or poor, in outline against the other soft tissues.

- iii even or uneven, in its distribution throughout the entire space enclosed by the joint capsule.

A tabulation of these 6 roentgenologic features, culled from the detailed readings, reveals a combination or grouping of the findings into a "pattern" that is distinct for each of the seven types of chronic arthritis studied. There follows below a summary to show the grouping of the roentgen findings in the characteristic arrangement for each type of arthritis. Incidentally the percentages in this summary refer to the number of patients in whom the findings were noted.

I. *Rheumatoid Arthritis*: 59 patients, 207 joints.

(1) Marked *general* decalcification (95 per cent) systemic, best seen in hands and feet.

(2) *Atrophic* loss of bone substance, "punched-out" areas (85 per cent), usually considered characteristic of gout; and cartilage destruction.

(3) Slight degree of soft tissue atrophy (33 per cent) or swelling (41 per cent) or both.

(4) *Effusion* that is dense (80 per cent), sharply outlined, often fusiform (73 per cent) and evenly distributed (70 per cent).

II. *Osteo-arthritis*: 312 patients, 52 joints.

(1) Slight degree of *general* systemic decalcification (75 per cent). This degree of systemic decalcification is essentially normal for this age period and occurs independently of any arthritic involvement. It is considerably less than the degree of systemic decalcification noted in rheumatoid arthritis.

(2) Marked bone production: lipping or osteophytes (100 per cent).

III. *Gout*: 12 patients, 21 joints.

(1) Atrophic loss of bone substance, "punched-out" areas (83 per cent.)

(2) Soft tissue swelling (67 per cent), that is circumscribed and eccentric to the joint.

(3) *Effusion* (75 per cent), that is dense (75 per cent), sharp (67 per cent), and uneven (75 per cent), and centered more on the area of loss of bone substance than on the joint space. The character of the swellings and effusions represents the most important difference between gout and rheumatoid arthritis.

IV. *Gonococcal Arthritis*: 11 patients, 12 joints.

(1) Marked soft tissue *swelling* which appears early and subsides rather quickly.

(2) Local decalcification (64 per cent) and

(3) Slight effusion (64 per cent), both of which decrease later.

(4) Moderate degree of *active* loss of bone substance (36 per cent) and thinning of the joint space (82 per cent).

(5) Comparatively early healing (few weeks or months) with bony or fibrous ankylosis (45 per cent).

Patients that have had gonorrhea may show lesions of another type, in the metatarsal-phalangeal joints, each joint showing atrophic loss of substance but with *no other change*, thus differing from rheumatoid arthritis in that there is no visible effusion, swelling or repair. In addition,

calcaneal spurs are present constantly, and are the type associated with gonococcal infections: vis., irregular in outline and density, and less sharply defined against the soft tissues than are the usual osteo-arthritic degenerative spurs.

V. *Tuberculous Arthritis*: 32 patients, 35 joints.

- (1) General decalcification (86 per cent) and
- (2) Local decalcification (82 per cent), both of which persist.
- (3) Marked *active* loss of bone substance (89 per cent) which occurs early and tends to be slowly progressive.
- (4) Soft tissue atrophy (75 per cent) and swelling (69 per cent) and
- (5) Effusion (82 per cent) which is constantly persistent, and is dense (75 per cent), sharp (61 per cent) in outline, and evenly distributed.

In tuberculous and gonococcal arthritis, the duration and severity of symptoms are of greatest importance in attempting to interpret the roentgen shadows in terms of joint pathology. Where a certain feature may be seen in a certain degree in both tuberculous and gonococcal arthritis, the duration of the lesion is apt to be 10 or 20 times longer in tuberculosis.

VI. *Marie-Strümpell Spondylitis*: 12 patients, 33 joints.

The findings in these cases are similar to rheumatoid arthritis except for distribution; and the atrophic loss of substance and soft tissue changes are not well seen because of the locality of the affected joints, in the spine.

- (1) General decalcification (92 per cent).
- (2) Calcification of the spinous ligaments (100 per cent).
- (3) Ankylosis (92 per cent) of the intervertebral facets and margins of the vertebrae, and frequently with obliteration of the sacro-iliac joints.

The "bamboo" appearance of the spine in these cases is well known.

VII. *Still's Disease*: 12 patients, 54 joints.

These findings are identical with the rheumatoid arthritis group, with the frequent addition of epiphyseal over-development because of the younger age of the patients.

In all types of chronic arthritis there may occur some degree of (1) local decalcification, (2) bone production, (3) narrowed joint space (cartilage destruction), or (4) ankylosis (in osteo-arthritis this occurs in the spine and sacro-iliacs only). General decalcification is frequent in osteo-arthritis (75 per cent) but it is of slight degree, and is normal for that age-period, whereas in rheumatoid arthritis (95 per cent) it is marked and extensive, and not accounted for by age-period changes. Atrophic loss of substance is as common in rheumatoid arthritis (85 per cent) as it is in gout (83 per cent). The soft tissue shadows are of utmost importance in roentgen diagnosis of arthritis and are frequently neglected. The hands and feet are the sites of choice to show detail in generalized roentgen changes, especially in rheumatoid arthritis. Antero-posterior and lateral views of corresponding joints of the extremities are necessary for determining the degree of decalcification and soft tissue changes. The roentgenograms may show little or no change in the early months of rheumatoid, osteo-arthritis, or Marie Strümpell arthritis, gout or Still's disease, but are important at this stage in the differential diagnosis of gonococcal and tuberculous arthritis. It is essential, for a rational interpretation of the roent-

gen shadows, that the roentgenologist know at least the *duration* and the *severity* of the joint symptoms. No single feature is diagnostic, but each group of these clinically typical cases has a basic pattern or grouping of roentgenologic findings.

In submitting these patterns of roentgen findings as being "characteristic" it must be emphasized that the observations and interpretations are based upon a much larger series of cases than are actually listed in the charts of this particular presentation. Regarding exceptional features in these patterns, such as the 13 per cent of local decalcification in rheumatoid arthritis, it must be understood that several joints were examined in most cases, and some of these joints may well have been affected by complicating factors such as trauma. In each case however there were usually one or two joints which conformed completely to the pattern described. Hence it is very important in the roentgenographic examination of a patient with polyarthritis to include more than one area. It is recommended that the hands, feet, knees and lumbar spine be examined routinely, regardless of the joints of which the patients complain.

It is to be noted that during the present study of these clinically typical groups the roentgenologists' diagnosis was in agreement with the clinical diagnosis in 100 per cent of the cases.

COMMENT

Osteo-arthritis and rheumatoid arthritis appear to be distinct entities by roentgenograms. Both osteo-arthritis and rheumatoid arthritis may occur in the same patient and in the same joint, and in such cases the characteristic changes of each type can usually be demonstrated in the same roentgenogram. The rheumatoid arthritis cases form one distinct group, with constant roentgen findings that do not suggest a further subdivision of this group. There appears to be some relationship, as yet unexplained, between Neisserian infection and arthritic changes, observed in:

(1) The metatarsal-phalangeal joints, (2) certain types of calcaneal sprus, (3) some types of spondylitis, and (4) possibly certain cases of rheumatoid arthritis.

Further details will be reported later, dealing with the correlation between early and late changes, between laboratory and roentgen findings, borderline and doubtful cases, and the findings in other types of joint lesions that may require differentiation from the commoner types of chronic arthritis.

CONCLUSIONS

1. Roentgenograms are the only non-surgical means of observing and recording the degree and progress of the destructive and ankylosing processes occurring in the joint tissues.

2. Roentgenograms, properly interpreted, are a most valuable aid to the differential diagnosis and prognosis in the various types of chronic arthritis.

THE PERIPHERAL BLOOD CIRCULATION IN CHRONIC ARTHRITIS AND THE INFLUENCE OF VASODILATORS

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Defective peripheral circulation and disturbed blood supply to the affected joints are apparent in many cases of chronic arthritis.

In considering peripheral circulation we must make a distinction between the circulation of the larger arteries, the veins and the minute vessels among which are included the capillaries, arterioles and venules.

Questions arise as to what part of the peripheral circulation is disturbed in chronic arthritis and which disturbance can be accounted for as an etiological factor and which can be assumed to be an aggravating agent.

ARTERIES

Wollenberg and Pemberton-Goldhaft reproduced in the joints of dogs and rabbits changes similar to hypertrophic arthritis, by ligating the vessels which carry the blood supply to the patella. This points to the obstruction of the larger arteries as an etiological factor. However, in the Vascular Clinic of the Post Graduate Hospital we have not observed chronic arthritis to occur in connection with endarteritis obliterans with the characteristic obstruction and impaired circulation. Bick reports from the Vascular Clinic of the Mt. Sinai Hospital of New York that of 32 cases of obliterative vascular diseases only one case showed signs of asymptomatic osteo-arthritis. It seems that in human beings the obliteration of major vessels has a more destructive effect on the tissues and does not produce chronic arthritis-like changes.

We see more frequently chronic arthritis associated with obliterations due to arteriosclerosis or diabetes. In these cases not only the larger vessels are involved but there is a generalized condition present of all the blood vessels, and apparently the involvement of the smaller vessels plays a more dominant rôle.

VEINS

The occurrence of disturbed circulation of the larger superficial veins in chronic arthritis is fairly well established. Bick and others have reported the finding of varicose veins in 77 per cent of osteo-arthritis and in 28 per cent of rheumatoid arthritis. We do not consider varicose veins as an etiological factor. On the other hand they aggravate the arthritic condition and their elimination is in every case beneficial to the patient. Inflammation of the veins, phlebitis, is often observed in the rheumatoid type of arthritis, but this is not a specific feature, but rather a complicating process of the rheumatic infection.

MINUTE VESSELS

More recent study and better understanding of the minute vessels

brings some light and a closer connection between the disturbed peripheral circulation and chronic arthritis.

Wright and Pemberton, Rhumann, Lunedei and Corradini and our observations all show that the disturbed circulation of the minute vessels frequently accompanies chronic arthritis and undoubtedly aggravates it.

Capillary and surface temperature studies carried out at the Vascular Clinic of the Post Graduate Hospital show that in over 50 per cent of chronic arthritics the blood flow is slow and the capillaries are constricted. In the rheumatoid type we found in 52.5 per cent small constricted capillaries, and there was slow blood flow in 65 per cent of the cases. In osteoarthritis the size of capillaries was small in 27.5 per cent, and there was slow blood flow in 52.5 per cent of the cases. A decreased number of capillaries we found only in the rheumatoid type of arthritis peripheral to joints with definite swellings, and in osteoarthritic patients with pronounced local tissue changes such as Heberden's nodes.

The surface temperature studies gave similar results. Wright and Pemberton found the surface temperature below normal in 62 per cent, Lunedei and Corradini in 70 per cent, and we in 52.5 per cent of the chronic arthritis cases.

All these observations of the impaired minute vessel circulation were made on the skin. Unfortunately, we are unable, up to the present time, to observe directly the blood circulation in the joint, but there are facts which point to a close connection and similarity between the minute vessel circulation of the skin in the extremities and in the joints. Chronic arthritis is often accompanied by cold extremities. We see it often connected with Raynaud's disease and scleroderma, in which conditions there is a definite proof of disturbed skin circulation. On the other hand, we find joint symptoms often in allergic skin disease.

It seems that the same nervous influence or chemical substances are responsible for the changes in the circulation of the minute vessels of the skin and joints and there is a parallelism in their action. Frequently a vasomotor instability of congenital or acquired origin is present.

The disturbed minute vessel circulation may possibly be considered as an etiological factor in chronic arthritis, although definite proof in this regard is still lacking. Undoubtedly it aggravates the arthritic condition and the progress of disease is directly influenced by the state of the blood circulation.

THERAPEUTIC CONSIDERATIONS

The practical application of these facts suggests strongly that special attention be paid to improving the peripheral circulation in the management of chronic arthritis. Age old empirical experience has shown the value of the different forms of heat treatments, massage, and exercises for this purpose. Hence these forms of treatment are well known and commonly applied.

Special attention has been paid in recent years to the effect of vasodilating drugs, such as choline compounds, histamine, and nitrates, to increase peripheral circulation. Heretofore it was found that many of these

drugs were ineffective when administered orally and produced only a brief dilation following subcutaneous administration. The vasodilating effect of nitrites appears limited to emergencies and they have not proved of any great value in the treatment of chronic diseases.

In order to obtain a more effective therapeutic result with vasodilating drugs the introduction of these drugs by iontophoresis was attempted recently.

By iontophoresis is meant the introduction of drugs through the skin through the polar effect of the galvanic (direct) current.

Table 1
Effect and dosage of vasodilating drugs by different methods of administration

Drugs	Acetyl-beta-methylcholine	Acetylcholine	Histamine	Nitrites
Oral	Mild general effect, lasts $\frac{1}{2}$ -1 hour. Dose: 100-200 mgm.	None	None	Powerful general effect, lasts 10 to 60 minutes depending on the drug.
Subcutaneous	Powerful general effect, lasts 15-20 minutes Dose: 5-25 mgm.	Mild general effect, lasts 15-20 minutes. Dose: 100-200 mgm.	Used only for tests. Dose: $\frac{1}{4}$ -1 mgm.	None
Intravenous	Dangerous, Toxic			
Iontophoresis	Pronounced general effect, lasts 20-40 min.	Mild general effect, lasts 10-20 minutes	No general effect.	
	Pronounced local effect, lasts 4-10 hours. Dose: 0.5-1 solution	Mild local effect, lasts 1-2 hours. Dose: 0.5-1 solution	Pronounced local effect lasts 2-4 hours. Dose: 1:20,000 solution	

Histamine iontophoresis was first introduced by Deutsch. His therapeutic results were favorable in muscular rheumatism, but were not satisfactory in chronic arthritis. The fact that histamine acts primarily on the capillaries and that acetylcholine-like chemical compounds are responsible for the dilatation of arterioles led us to attempt iontophoresis⁹ with choline compounds. The usefulness of acetylcholine to increase peripheral circulation has been limited by the fact that it is rapidly destroyed by body fluids and blood. Recently another compound of choline—acetyl-beta-methylcholine chloride—synthesized by R. T. Major, has been found to offer greater possibilities of clinical usefulness. It is destroyed more slowly in blood and body fluids, is more potent, and lacks almost entirely certain undesirable by-effects of acetylcholine.

Table 1 explains the effect of vasodilating drugs by the different methods of administration.

TECHNIQUE OF IONTOPHORESIS WITH VASODILATORS

A one per cent solution of acetyl-beta-methylcholine chloride (1 gm. in 100 c.c. of water) is employed. The drug being an alkaloid with a posi-

tive charge, can be introduced into the tissues from the positive pole only. Reinforced asbestos fabric paper is saturated with the solution and wrapped around the affected joints. A fairly large malleable metal plate is placed over the wet asbestos paper and connected to the positive pole of a galvanic generator. A well wetted very large pad electrode is employed as the dispersive electrode and after applying low on the back or abdomen is connected with the negative pole.

The current is turned on first to a strength of a few milliamperes only and then is slowly increased to 20-30 milliamperes, always being kept within the patient's tolerance. Treatments of twenty to thirty minutes duration are employed. To avoid the possibility of burns, care must be taken that the metal electrode or electrode clamps do not come in

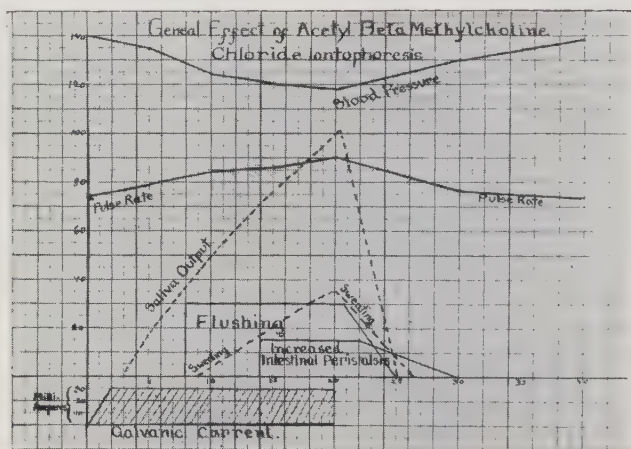


Fig. 1.
General effect of acetyl-beta-methylcholine chloride iontophoresis.

direct contact with the skin. The asbestos paper is more satisfactory than gauze or blotting paper for it absorbs less fluid, is stronger, and keeps moist for a longer time. Two regions of the body may be treated at the same time, with the help of a bifurcated cable from the positive pole. At the end of the treatment the current is slowly turned off and after the removal of the electrodes the part is dried and kept covered. Patients receive for the first three to four weeks two treatments weekly, later one. In histamin iontophoresis a 1:20,000 solution is employed or an impregnated special foil marketed under the name Katexon. The drug being more irritating only 6-10 milliamperes of current is used for 1-10 minutes duration.

The physiological effect of acetyl-beta-methylcholine chloride and histamine iontophoresis is quite different. Histamine iontophoresis does not produce any general effect and acts only locally on the capillaries (table 2).

Acetyl-beta-methylcholine iontophoresis produces, besides a pronounced local effect, also a general effect. This effect is similar to that produced by the subcutaneous administration of this drug but occurs in prolonged and milder form (fig. 1, table 3).

THERAPEUTIC RESULTS

Fifty-two chronic arthritis patients have been treated. Of these there were thirty cases of rheumatoid arthritis and twenty-two cases of osteoarthritis. Most of these cases were patients who had previously had, in addition to general treatment, all other kinds of local treatment, such as diathermy, short wave fever treatment, x-ray treatment, etc., without relief of pains or improvement of symptoms. We did not change the form of general treatment, as we wished to gain a clear picture of the reaction to iontophoresis.

A definite reduction in pain, swelling, stiffness, with increase of function and lessening of deformities was required in order to recognize the result obtained as a definite improvement only.

Most promising results were obtained in stubborn cases of rheumatoid arthritis; 90 per cent of these cases showed improvement. The usual complaint of the patients of cold hands and feet was frequently relieved after

Table 2

Physiological effect of acetyl-beta-methylcholine chloride and histamine iontophoresis

Drugs	Acetyl-beta-methylcholine chloride	Histamine
General effect	Flush, sweating, increased salivation, lowered blood pressure, increased pulse rate, increased intestinal peristalsis, increased metabolism. Effects last 20-40 minutes.	None
Local effect	<i>Action mostly on arterioles,</i> Increased skin temperature for 2-8 hours, Increased sweating for 4-10 hours, Goose-flesh lasting 10-20 minutes, Increased oscillometric reading, Faster capillary flow, Slight redness, Slight increase in local white blood cell count	<i>Action mostly on capillaries,</i> Increased skin temperature for 2-4 hours, Enlarged capillaries, Increased capillary permeability, Wheal formation, Faster capillary flow, Definite redness.

a short period of treatments, and simultaneously the swelling of joints and the feeling of stiffness decreased, and their mobility increased, and pains disappeared. These good results were anticipated in rheumatoid arthritis because this is the type of arthritis in which we have found the most pronounced circulatory disturbances. Most of the rheumatoid patients had long-standing disease, with the characteristic picture of spindle-shaped phalangeal joints, definite swelling of the knees and ankles with deformities and limitation of function of the joints. All of these signs improved greatly under iontophoresis. In two cases where rheumatic nodules were present the nodules became smaller. Two cases of Dupuytren's contracture improved markedly, and in one case the patient regained the full use of her hand. In two cases of rheumatoid arthritis where elevation of temperature was constantly present the patients did not respond favorably.

In the osteo-arthritis type the results were also encouraging. We must admit, however, that in this type of arthritis similar results were ob-

tained with usual therapeutic measures such as heat, diathermy, massage, etc. With acetyl-beta-methylcholine chloride iontophoresis there was an improvement in 80 per cent of the cases.

In both types of arthritis where the patients had definite joint-swelling a reduction of the swelling and an increased capillary circulation were observed after iontophoresis. Further studies are necessary to determine whether the increased capillary circulation is responsible for the reduction of swelling or whether the reduction of swelling in itself through relieving the tension of the tissues is responsible for the improvement of the capillary circulation. The therapeutic effect of this form of

Table 3

The immediate changes in metabolism, circulation and blood after acetyl-beta-methylcholine chloride iontophoresis

	Immediately Before treatment	Immediately After treatment
Metabolic rate (Subject J. H.)	+4	+ 55
Oscillometric readings (Subject J. G.)	1 (1. femoralis)	2.5 (1. femoralis)
Electrocardiogram (Subject J. H.)	Normal tracing	PR conduction time increased. T wave am- plitude increased. Rate slower
Sedimentation rate		No changes
White blood cell count (Subject J. H.)	6850	9750
Blood chemistry: Calcium Chloride Cholesterol Phosphorus Sugar Carbon dioxid	No immediate changes	

treatment might be explained by the deposition of the drug in the superficial tissues and its slow absorption from there, giving prolonged slight general vasodilation, combined with a pronounced and prolonged local effect.

Iontophoresis is contraindicated in patients who show constant elevation of temperature, also in cases complicated by asthma. Caution must be exercised and shorter treatments given to patients with heart involvement and to old persons in a feeble condition.

COMMENT

In spite of the definite physiological effect and the favorable therapeutic results, we must confess that we still do not know precisely how much of the drug is absorbed by the tissues with the iontophoresis method or how deeply the drug penetrates. Further investigation is needed to ex-

plain the definite mode of action of acetyl-beta-methylcholine chloride iontophoresis on the local circulation and sweat glands.

That the effect of acetyl-beta-methylcholine chloride iontophoresis is specific and not a simple galvanic effect was demonstrated in the following way: both hands of a patient were treated at the same time—one hand with the drug and the other with normal salt solution. Both hands were connected to the positive pole with the help of a bifurcated cable. The indifferent negative electrode was at the back. After 20 minutes treatment with a galvanic current of 20 milliamperes strength the hand with normal salt solution remained cold. There was no sweating, only a slight redness in patches, and the capillary picture remained unchanged. The hand treated with the drug showed all the characteristic symptoms of acetyl-beta-methylcholine chloride iontophoresis: increased skin temperature, sweating, gooseflesh, faster capillary flow and a slight diffuse redness.

Animal experiments (table 3) corroborated the specific effect of acetyl-beta-methylcholine iontophoresis. The blood pressure dropped only when the drugs were inducted from the positive pole. Connected with the negative pole, or using normal saline solution instead of the drug did not produce any changes in the blood pressure.

Metabolic tests carried out by Dr. Wilbur Duryee of our clinic also prove the specific effect of the drug. The galvanic current with saline solution did not produce any changes in the metabolic rate. Acetyl-beta-methylcholine increased the metabolic rate from plus 4 to plus 55. Both experiments were made on the same patient under identical conditions.

This presentation is not an attempt to create the impression that acetyl-beta-methylcholine chloride iontophoresis is a specific therapy for chronic arthritis. But the fact that more than 50 per cent of chronic arthritis patients have an impaired minute vessel circulation and acetyl-beta-methylcholine chloride iontophoresis improves the general and local minute vessel circulation—directs attentions to acetyl-beta-methylcholine chloride iontophoresis as an important factor in the therapy of arthritis.

CONCLUSIONS

1. There is a close relation between chronic arthritis and impaired peripheral circulation with disturbances of the minute vessel circulation most pronounced. Over 50 per cent of chronic arthritic patients reveal disturbances in the minute vessel circulation.

2. Experiments and therapeutic results demonstrate that vasodilating drugs can be introduced into the system by means of iontophoresis and may be used more satisfactorily by this method than by oral or subcutaneous administration.

3. Acetyl-beta-methylcholine chloride iontophoresis appears to be of value in the therapy of chronic arthritis, especially in the rheumatoid type.

DISCUSSION

DR. PHILIP S. HENCH, Rochester, Minnesota: Dr. Kovacs contends that there are significant alterations in capillary blood flow in both atrophic and hypertrophic arthritis; that these alterations may be of etiologic importance and that most patients are materially improved when these alterations are corrected at least in part. We agree that arthritis is not primarily associated with occlusive vascular disease of large vessels. At the Clinic

we have never seen a related arthritis among a large number of cases of thrombo-angitis obliterans. In a number of rheumatic diseases pathological changes in small vessels are found. In chronic atrophic arthritis there are often very obvious alterations in general blood flow: low blood pressure, cold clammy extremities, lowered skin temperature.

Dr. Kovacs and others anticipate constricted capillaries in the nail-bed of the arthritic. At the Clinic Dr. George Brown, Miss Roth and I have studied the capillary flow in a large number of cases of atrophic and hypertrophic arthritis. Like Prusik, we have been unable to find consistent alterations. In many cases the size of the capillaries is unaffected or slightly dilated, not constricted. Often, however, their flow is slow. Some arthritics exhibit vasomotor alterations long before the onset of their joint symptoms. Others develop them fairly early in the course of their disease. Many severe cases exhibit them rather late. The fact remains that the alterations are not consistently present and during the past five years while selecting cases suitable for sympathectomy we have seen many patients with marked and even advanced arthritis with warm extremities and no changes in capillary size or flow. Dr. Kovacs himself finds changes in only about half of those with atrophic, and about one-fourth of those with hypertrophic arthritis.

Dr. Kovacs is wisely conservative in ascribing definite etiologic significance to alterations which occur so irregularly and inconsistently. It has been an attractive idea that arthritis is the result of blood hunger, that the changes in joints are secondary to an inadequate blood supply. We must distinguish between atrophic and hypertrophic arthritis. Recall that when patellar vessels are ligated and the blood supply sharply diminished, resulting alterations in bone are chiefly hypertrophic not atrophic. This is what one should expect if one accepts the recent dictum of Jones and Roberts that bone undergoes increased calcification if its blood supply is decreased. But it undergoes decalcification if its blood supply is increased. If this be true one might better search for an augmented not a decreased blood supply to account for bone atrophy in atrophic arthritis, and indeed such a state has been suggested as being present in the form of hyperemia and new vessel formation.

Raynaud's disease presents an outstanding example of diminished blood supply from vasospasm. If vasoconstriction were the cause of arthritis isn't it strange that arthritis occurs in less than 5 per cent of cases of Raynaud's disease? Since vasomotor changes are so consistently present in chronic arthritis—early in one, late in another, not at all in a third—they must represent not the cause of the disease, not even an essential part of the disease but a complication appearing at varying times and in varying degree as perhaps the sympathetic nervous system is variously affected by the "toxins" of the disease. As Dr. Kovacs pointed out an interpretation of alterations in nail bed capillaries can only be made with consideration of the age grouping. What we need even more than this is a study of capillaries correlated to the localization, duration, and severity of the disease.

Whether such alterations are of primary or secondary significance their recognition and correlation may be important. An army harassed by fierce encounter at the front is in trouble indeed if its lines of communication become narrowed or obstructed. An arthritic joint is in trouble indeed, its job is hard enough without having its lines of defensive communication interfered with by some complicating circulatory abnormality. Cause or complication, a significant alteration in circulatory tone must be corrected and Dr. Kovacs' search for some simple method of providing a prolonged improvement in vascular tone is highly commendable.

I have not used iontophoresis and cannot discuss its merits. I am sure that Dr. Kovacs will agree that while iontophoresis may be effective, our ultimate goal is some method of vasodilation requiring neither the cutting of sympathetics nor the use of electric machines beyond the financial province of most patients. The work of Starr and more recently of Goldsmith in Rochester indicates that mecholin given orally in much larger doses than Dr. Kovacs used produces fairly prolonged significant vasodilation. The effects of such doses should be compared to iontophoresis. When I suggest the desirability of vasodilation, I do not necessarily mean capillary vasodilation, arteriolar vasodilation is preferable. They are not the same and I think we should not lay too much stress on the significance of capillary constriction or use capillary vasodilation as an infallible criterion of improvement. Skin temperature is dependent on arteriolar tone, not capillary tone. Cold clammy hands signify arteriolar, not necessarily capillary constriction. Indeed the capillaries may be dilated although their flow is sluggish. The size of capillaries is relatively unimportant as their tone is dependent on the state of the arteriolar circulation. Fix the arterioles and the capillaries will take care of themselves as is demonstrated after sympathectomy when in the presence of arteriolar dilation and an improved flow, the capillaries are not more but less dilated than before operation.

DR. IRVING S. WRIGHT, New York: One of the most interesting observations of Dr. Kovacs and others is that arthritis rarely occurs in cases of occlusive vascular disease. Where the obstruction to blood flow to a part is sudden or gross, arthritis is not produced. Occlusive disease of large vessels is not a causative factor in arthritis. Studies on the size and flow of capillaries as made at The Mayo Clinic, also by us and others, lead us to feel that capillary alterations are not the cause of arthritis although they frequently accompany it. At any rate from studies of surface capillaries and skin temperature it is impossible to draw definite conclusions as to the condition of articular circulation. Dr. Kovacs' revival of an old method of treatment is worthy of careful consideration and my own observations indicate that the effect of these drugs by means of iontophoresis is more prolonged than by the oral or hypodermic route. Dr. Kovacs has made no claim as to the curative value of mecholin iontophoresis, but if it will relieve pain and discomfort it has a rightful place in therapy. In considering the high percentage of results one must remember that the psychological effect of a rather elaborate technic may be very definite. Further time and work will be necessary to determine the permanence of its effects.

DR. D. E. KAUFMAN, St. Louis, Mo.: I have used mecholin in twenty-three cases of chronic arthritis with benefit to large joints, but none to small joints, such as those of fingers and wrists. In six cases the knees have been very gratifyingly benefited by treatments three times a week.

DR. KOVACS, New York: I agree with Dr. Hench that the impaired capillary circulation cannot be accounted for as an etiologic factor in chronic arthritis. On the other hand, it has been found, in more than half the cases of arthritis, that there is an impaired capillary circulation aggravating the arthritic condition. Relieving it, one surely benefits the patient. The simplest way of medication is oral administration, I admit, but the simplest method is not in every case the most satisfactory one. The large doses administered by Goldsmith seem to me to be quite expensive therapy. The need for these large doses proves that most of the drug is destroyed in the stomach before it is absorbed, and the part that gets in the circulation causes a mild, general vasodilatation. In arthritis, one needs primarily to increase the local circulation of the affected joint or joints, and iontophoresis seems to me the most adequate method for accomplishing this. I usually administer treatment twice a week and have had better results on small joints. It increases, first of all, the circulation of the affected joints and produces only a slight, general reaction. I agree with Dr. Wright that further time and work will be necessary to determine the permanence of acetyl-beta-methylcholine chloride iontophoresis. Dr. Kaufman's observations prove only that there is still a large field unexplored, and much more work must be done before the therapeutic effects of acetyl-beta-methylcholine chloride iontophoresis can be fully evaluated.

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NUTRITIONAL FACTORS IN CHRONIC ARTHRITIS*

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The attention drawn to the constitutional conception of chronic arthritis in 1931 provided an incentive for continuing in this special field certain dietary studies which had been carried on for several years in the more general field of nutrition. Since then, study has been devoted to the many

Table 1. An example of one sheet from the week's diet record of a patient

HENRY FORD HOSPITAL		Date: March 28 Case No. 186612					
Name—A. H.	Daily Diet Record—OPD						
Foodstuffs	Serving amts.	Grams	P	F	C	Cal.	
MORNING MEAL							
Soft fried egg	1		6	6			
Toast	1½ slices	4.5	4.5	—	22.5		
Butter	½ square	5	—	4.2	—		
Sugar	1 teaspoon	5	—	—	5		
Cream	1 tablespoon	15	.4	3	.6		
Coffee	1 cup						
			10.9	13.2	28.1		
NOON MEAL							
String beans with milk	4 tablespoons	150	2.2	—	4.5		
	(Milk)	50	1.5	2	2.5		
Hash	2 tablespoons						
	(Potatoes)	50	1	—	9		
	(Meat)	50	11	12.5	—		
Bread (home made)	1½ slice	15	1.5	—	7.5		
Butter	¼ square	2.5	—	2.1	—		
Layer cake, chocolate frosting	1 piece (small)	100	7.6	14.8	58.6		
Tea	1 cup						
			24.8	31.4	82.1		
EVENING MEAL							
Mashed potato	4 tablespoons	200	4	—	36		
Fried parsnips	6 pieces (3 x 3 in)	150	6	8.5	22.5		
Bread (home made)	½ slice	15	1.5	—	7.5		
Butter	½ square	5	—	4.2	—		
Salad—apple, date and nut	4 tablespoons		1.9	23.6	15.3		
Water	½ glass						
Lettuce	1 leaf	30	.4	—	.9		
			13.8	36.3	82.2		
EXTRAS							
Water	1½ glass						
Apple	1	150	—	—	22.5		
Chocolate candy bar	1 (4 x 1¼ x ½ in)	60	4.8	21	30.7		
			4.8	21	53.2		
TOTAL FOR 24 HOURS			54.3	101.9	245.6	2118	

*From the Department of Medicine, Henry Ford Hospital.

contributing factors concerned in chronic arthritis, notably the hereditary, nutritional, metabolic, mechanical, nervous and infectious. The consistency of the abnormal findings under these headings has been impressive, as has been the response of the disease to corrective measures based upon them. Of special interest were the nutritional factors, of which the dietary features provide the topic of this presentation.

The first aim was to learn the established eating habits of patients with chronic arthritis. Previous experiences had already demonstrated that the real truth could be obtained only by a record of an individual's actual intake when he was following his natural inclinations in his own home environment. Accordingly, patients were given a week's supply of blank forms constituting a diet diary, with detailed instructions to record in ordinary household measures all items of food taken.

In table 1, the dietitian has converted the ordinary household measures into grams and has estimated the protein, fat and carbohydrate content for each foodstuff, as well as the total caloric value for the day. From

Table 2. Assembled data for the seven day period of a diet diary.

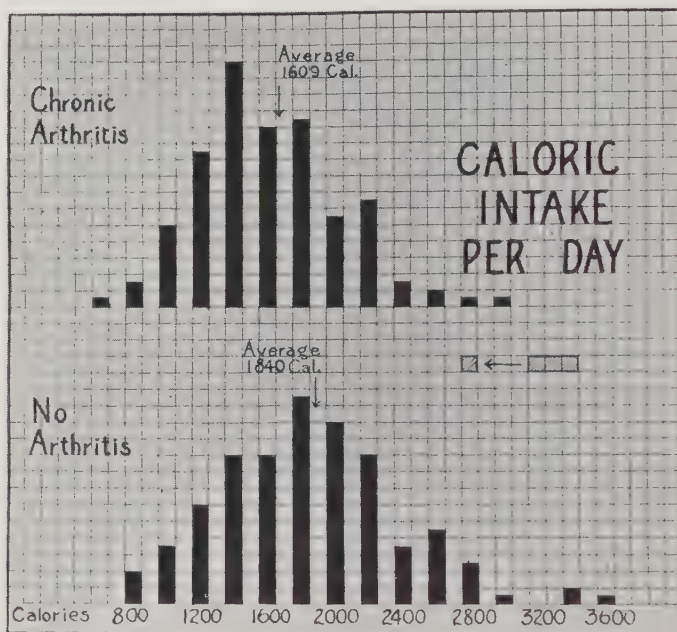
	1933		CAL.		P.		F.		C.
Mar. 23	—	1840	—	67	—	80	—	213	
24	—	2061	—	64	—	73	—	287	
25	—	1976	—	64	—	100	—	205	
26	—	1814	—	55	—	82	—	214	
27	—	2083	—	71	—	95	—	236	
28	—	2118	—	54	—	102	—	246	
29	—	1554	—	49	—	58	—	209	
Average		1921	—	61	—	84	—	230	

seven such records, data were assembled to cover a seven-day period. Table 2 represents a summarization of such a week's figures. The wide range of variation from day to day illustrates the error which would occur if any single day's intake were utilized as an index to the patient's established habits. The longer the period of time represented, the more truly expressive is the result. Arbitrarily, a week has been chosen as a unit of time for such records, and for purposes of comparison a one-day average has been created in each instance to represent the values of the seven-day period.

The results of this type of record have been compared to estimations based on the story of the patient, to the demonstration of the greater accuracy of the former. In addition, it has been felt that this method of investigating an individual's actual habits of eating has in it even greater truth than do weighed records of diets obtained during a patient's hospital stay, because at home the customary market purchases and kitchen provision cater to the patient's usual desires with a more natural range of choices than is provided by the institutional dietary.

The information resulting from these studies has been surprising. In chart 1, the caloric intake per average day per patient in a group of 138 cases of chronic arthritis, hypertrophic and atrophic, in proportion of nine to one, has been compared to that of a group of 148 patients without arthritis. Considering the range of distribution in this chart, the majority of the cases of chronic arthritis had an intake per day falling between 1200 and 1800 calories, with an average of 1609 calories. In the group of 148 cases without arthritis there was a shift to the larger values, between 1400 and 2200 calories per day, with an average of 1840 calories. The question of

Chart 1. Comparative record of caloric intake per day in groups of cases with chronic arthritis and without chronic arthritis.

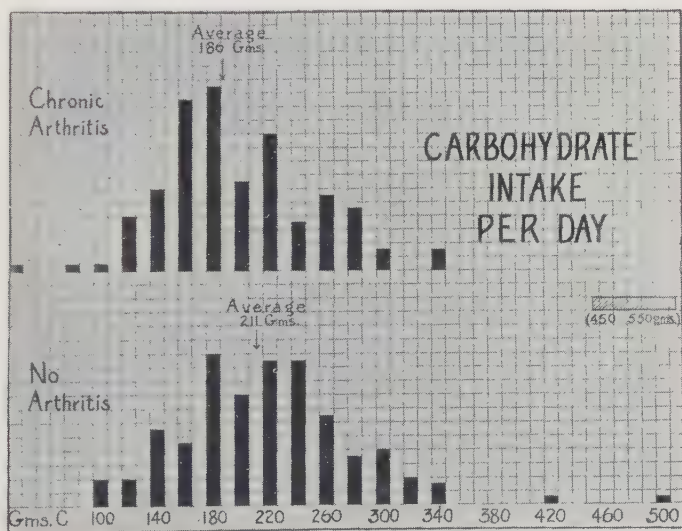


body weight in relation to caloric intake will be presented elsewhere. The fact, however, that the average weight of the arthritic patients was 66.1 kilograms and that of the non-arthritic patients was 67.0 kilograms makes it evident that the difference in caloric intake in the two groups was not a matter of relationship to the difference in body weight.

If standards for an average individual may be referred to, according to the often-quoted statements of Rubner, Voit, and others, based on statistical investigations, a man of 70 kilograms weight at light work requires an intake of 3200 to 3400 calories a day. Alonzo Taylor has more recently predicated that, in view of decreasing amount of work and increasing consumption of fruits and vegetables, the allowance of 2800 calories a day would be reached in about two more generations. The figures in chart 1 taken under natural circumstances, and in a group of active individuals of the schoolteacher, office worker, housekeeper, "white collar" class, are surprisingly low.

Every precaution possible has been taken to make these records reflect the truth. First, the patient has been warned to adhere to natural habits of eating; the very keeping of the record is so disciplinary that patients are apt to be on their guard to attempt to make a better showing than is natural and so to modify their diet according to their own ideas or what they may have heard from others. They were urged, however, in preference to hiding their indulgences, to make them clearly evident. Second, each diet diary has been critically reviewed with the patient who submitted it. If there was any suggestion of incompleteness, or if anything occurred during the week of record to modify the patient's ordinary habits, the diet diary was repeated. In fact, the accustomed followup has resulted in a repetition in almost every case. Care has been taken to insure that everything of food value was included in the records, such as butter on bread or on vegetables, sugar and cream in coffee or on cereals, food taken between meals or in the evening, and even sweet drinks and chewing gum. Third, it must be

Chart 2. Comparative record of carbohydrate intake per day in groups of cases with chronic arthritis and without chronic arthritis.



acknowledged that the tables used in interpreting food values are only approximately accurate and that opportunity for inaccuracy exists in the utilization of household measures as units for recording food intake. As a check upon this latter factor, a group of thirty-four in-patients were allowed to select freely from the hospital "full diet" list, and an accurate record was kept of the weighed intake for an average of seven days per case. In these instances, the average intake was 1678 calories per day. This suggests, at least, that the surprisingly low figures for caloric intake have not been due to the manner in which records have been kept by patients.

It was, of course, important to determine and compare the sources of the caloric intake in the two groups of patients. In the arthritis cases, on the average, 52 grams of proteins were taken per day; in non-arthritis cases,

60 grams. Fat averaged 73 grams per day for arthritis cases, 84 grams per day for cases without arthritis. In terms of percentage of total calories, protein supplied 12.9 per cent in the cases of arthritis, and 13.0 per cent in the cases without arthritis, while fat supplied 40.8 per cent in the cases of arthritis and 41.1 per cent in the cases without arthritis.

Of particular interest were the figures representing the carbohydrate intake, since so much attention has been paid to this factor in recent dietary work on arthritis. It is evident in chart 2 that the majority of patients in the group with chronic arthritis had a daily average carbohydrate intake of between 160 and 220 grams, with an average of 186 grams per day for the group. The majority of patients without arthritis showed a daily average of carbohydrate consumption between 180 and 260 grams, with an average of 211 grams per day for this group. Interpreting these average

Table 3. "Partitioning" of carbohydrate intake of the seven days period represented in table 2.

	1933	C.	REF. UNR.		POT.	VEG.	FRT.	MLK.
			SUG.	CER. CER.				
Mar.	23—213—	7%—39%—1%—34%—	1%—16%—	2%				
	24—287—	5%—51%—7%—23%—	4%—8%—	2%				
	25—205—	2%—55%—0	—14%—	7%—11%—11%				
	26—214—	14%—50%—0	—13%—	3%—12%—8%				
	27—236—	14%—56%—0	—12%—	3%—10%—5%				
	28—246—	14%—40%—0	—18%—11%—15%—	2%				
	29—209—	14%—42%—1%—13%—	3%—22%—	5%				
Average	230—	10%—48%—1%—18%—	5%—13%—	5%				

values in terms of the percentage of total calories supplied by carbohydrates, the figure is 46.2 per cent for patients with arthritis as compared to 45.9 per cent for patients without arthritis.

The evidence so far presented certainly does not lend support to a belief that persons with chronic arthritis have been accustomed to a dietary which is indulgent in any respect.

Further studies relating to carbohydrates were carried out, suggested by the common story of craving for sweets, or inordinate eating of bread or potatoes. The individual items making up the carbohydrate intake of each day of the diet diary records were classified, as illustrated in table 3, under seven headings. (1) The column labelled sugar includes all sweets. (2) The column labelled refined cereals includes all products of white flour and other milled cereals. (3) The column labelled unrefined cereals includes all whole-grain cereals and their products. (4) The column labelled potatoes needs no comment except that they were separated from other vegetables because of their high starch content and because of the fact that much of their content of vitamins and minerals is lost in the usual methods of kitchen preparation. (5) The column labelled vegetables in-

cludes all except potatoes. (6) The column labelled fruits is self explanatory. (7) The column labelled milk includes all dairy products which are a source of carbohydrate. The percentage of the day's carbohydrate represented by foods in each of these seven groups was recorded.

The percentages represented under these seven headings were combined into two main divisions, one representing the protective foodstuffs, which supply carbohydrate plus minerals, vitamins, and bulk, and the other representing the non-protective foodstuffs, which supply carbohydrate alone or nearly alone. Fruits, vegetables, unrefined cereal products and dairy products comprise the protective group; sugar, refined cereals, and potatoes make up the non-protective group. Thus, in the example given in table 3, an average of 24 per cent of the total carbohydrate for the week was derived from protective foods, whereas 76 per cent came from non-protective foods. This survey, relative as it is, serves as a rough and accessible measure of vitamin and mineral intake. Obviously it does not in any way account for vitamins and minerals contained in foods primarily protein or fat in nature. It might be added, parenthetically, that further analysis of the diet records from the standpoint of types of food providing protein and fat was carried out in a number of cases; it was felt that for practical purposes a satisfactory estimate was had from this method of "partitioning" the carbohydrate foods alone, however.

When this method of study was applied to the diet diary records of the patients referred to above, it was soon evident that in patient after patient the protective foodstuffs formed the source for one-tenth to one-third of the total carbohydrate, while the major part of the carbohydrate, two-thirds to nine-tenths, was obtained from concentrated and refined foodstuffs. The significance of this finding has already received emphasis in those contributions which suggest a certain optimum vitamin and mineral intake as necessary for maximum efficiency.

When the constancy of this finding became apparent, a natural therapeutic experiment took form. The results of the survey of the natural habits of eating were gone over in detail with each patient, and directions given to modify the dietary by using more fruits and vegetables, by increasing the consumption of dairy products, and by substituting unrefined cereal products for the milled cereals. The greatest emphasis was laid upon decidedly increasing the fruit and vegetable intake. A simple diet booklet was prepared, in order to make easier the plan of eating which attained these objectives, and to avoid resorting to any stereotyped diet lists of permitted and forbidden foods. Underlying principles were stressed, rather than individual items. Patients have had plenty to eat, the difference being the placing of emphasis in a new direction. The transition and progress have been checked by repeated diet diaries.

Over a two year period, patients who have followed this advice have shown unmistakable evidences of marked constitutional change. Not only has the improvement occurred in joint manifestations and in bowel function as reported by others, but in addition significant changes occurred in the less easily measured qualities of well-being and resistance. Weight changes have usually occurred, even when not sought. On the same plan

some underweight patients have gained to a new level. Other patients who were overweight have lost. The important feature in common has been that a new weight level was reached, and then stabilized, which seemed to be indicative of a state of greater efficiency in the individual patient.

This hidden error in diet has been found in other patients than those with arthritis but the significant fact in the arthritic group is the satisfactory response and improvement in the constitutional as well as the local manifestations of the disease.

SUMMARY AND CONCLUSIONS

1. A method has been presented for obtaining a comprehensive survey of established habits of diet of patients in their home environment.

2. Surprisingly low figures for total caloric intake have been found in the types of patients studied, averaging 1609 calories per day for patients with chronic arthritis and 1840 calories per day for patients without arthritis.

3. It is not apparent in the cases studied that persons with chronic arthritis have been accustomed to a dietary indulgent either in total calories or the quantity of carbohydrate.

4. A method is suggested which uncovers as a hidden dietary error a relative deficiency in protective foodstuffs.

5. With other factors cared for, this particular attention to the nutritional state in chronic arthritis has brought more satisfactory results, both constitutionally and locally, than have been obtained otherwise.

DISCUSSION

DR. ROBERT B. OSGOOD, Boston: Attention should be called to the great disparity of ratio between 128 cases of hypertrophic arthritis and 10 cases of atrophic arthritis of Drs. Sladen, Ensign and McColl. I have been inclined to believe that the influence of diet was greater in the atrophic than in the hypertrophic type and that the matter of quality was more important than quantity. This study suggests that quantity is important, especially of what they properly call "protective food stuffs" which most of us speak of as vitamins. A lack of protective foods in effect constitutes a deficiency diet. What Minot has spoken of as an "optimum diet" is still of great importance in the therapy of chronic arthritis and most earnest attempts should be made to determine what constitutes such an optimum diet, not for both types or even for one of the other type, but for each individual who is suffering from the disease. It would seem wise not to attempt any rigid standardization of diet, but to study the alimentary aberrations of each patient and strive to meet their individual needs of both optimum intake and efficient outgo.

THE INFLUENCE OF DIETETIC AND OTHER FACTORS ON THE SWELLING OF TISSUES IN ARTHRITIS

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Peirce and Pemberton reported data indicating that, following a stab of the finger, a lesser number of red cells per cubic mm. exists in blood first issuing from the peripheral tissues of patients with severe arthritis, than in later issuing blood. While this difference sometimes obtains among normal persons and patients with mild arthritis, it does so with less frequency. Several possible explanations of this phenomenon were advanced; namely, that the capillaries of normal persons are open in larger numbers; that the first issuing blood in arthritics is diluted in the vessels; and that the normal or decreased number of cells in the vessels is scattered and dispersed through increased or normal amounts of serous fluids from the tissues as they issue forth.

With the aim of exploring the last mentioned possibility, an attempt was made by Peirce, Wright and Pemberton (unpublished data) to determine the rapidity with which normal salt solution injected intradermally in the arthritic would be absorbed as compared with normal persons. McClure and Aldrich have shown that in the presence of edema there may be an apparent "avidity" of the tissues for fluid such that, contrary to expectation, normal salt solution injected intradermally disappears more rapidly from the tissue. The results of these experiments, however, were not sufficiently clear-cut to permit of precise evaluation and further observations are pending. The general problem involved, however, has been brought to the fore again by other considerations which will be briefly discussed.

In a recent publication Pemberton, Peirce and Bach have adduced evidence indicative of the prompt subsidence of the inflammatory or swollen tissues of the arthritic following dietetic control in suitably selected cases. The statement was there made that a response of this nature is probably to be observed more promptly under these circumstances than following any other line of therapy, with the possible exception of convalescence following the removal of focal infection in very early sthenic cases. Changes may be observed as early as twenty-four hours following the institution of dietetic therapy and may become very graphic at the end of three or four days. The matter has also been previously stressed elsewhere (Pemberton).⁸

In conjunction with his associates, one of the present writers has published a considerable series of studies indicating that various physiological disturbances accompany or characterize arthritis, and the American Committee for the Control of Rheumatism has expressed itself as believing that arthritis in general is a systemic disease with joint manifestations. Furthermore, in many cases of arthritis the phenomena within and around

the joints are almost negligible, being greatly over-shadowed by such clinical states, with the involvement of other tissues, as come under the head of myositis, neuritis, disease of the uveal tract, mental hebetude, fatigue, neurasthenia and even psychoses.

Viewing a series of arthritics undergoing successful therapy, especially along nutritional lines, and having the above several considerations in mind, certain clinical phenomena are to be observed, the possible significance of which has apparently largely or wholly escaped notice. These phenomena consist first in the subsidence of supposedly inflammatory tissue along the proximal and middle phalanges of many or all fingers and in the subsidence of swelling on the dorsum of the hand, beginning on the ulnar aspect. Subsidence of the swollen tissues surrounding the shafts of the phalanges may give rise to a relative increase in prominence of articular and periarticular enlargements at the phalangeal articulations, especially in the hypertrophic type. Subsidence of the dorsal tissues of the hands, however, leads to a collapsed or "all gone" appearance which renders visible, slowly but progressively, the tendons of the metacarpus.

While the collapse of tissues is evident to a critical observer it is difficult to obtain striking photographic illustration of the subsidence of swelling.

There takes place at the same time a progressive recession of swelling, in the dorsal tissues of the hand, from the metacarpo-phalangeal articulation toward the carpus itself. At a certain stage of subsidence, the metacarpal tendons may be uncovered across the dorsum of the hand from the knuckles to a point midway between the knuckles and the wrist. The residual zone of swelling, above this point, more or less like a bracelet which has slipped down upon the hand, in turn slowly recedes upward until inspection and palpation of the hand as a whole reveal nothing but the underlying bony and tendinous structures covered by the integument itself. Conversely, exacerbations of the "arthritis" have been observed to be accompanied by a return of swelling in the "non-articular" soft tissues. The process under discussion is most evident at an intermediary stage when there is contrast present between the subsided and the unsubsided tissues. The possibility of such a subsidence on the dorsum of the hand may not suggest itself at the outset, as the hand does not necessarily or usually "appear" swollen. Similarly, the appearance after loss of swelling is normal and no residual marks of previous pathology are left. Thickness and swelling of the metacarpophalangeal articulations, when present, likewise undergo retrogression. There is therefore a fairly close correlation between the activity of the arthritic process and the phenomenon of tissue swelling. This question is detailed at some length because it is believed that it has not been the subject of adequate scrutiny.

The nature of the swelling above referred to awaits explanation. Inasmuch as the tumefaction also concerns regions, such as the dorsum of the hand, where there are no joints, it must be regarded as something partly extraneous to the joints themselves. Furthermore, these regions are not the seat of pain such as usually characterizes the joint structures themselves in the course of arthritis. The thought suggests itself therefore that the

condition under observation reflects a systemic disturbance which indeed, does not partake of an inflammatory nature in the sense usually understood by that term. The motility of the swelling suggests further the possibility that it may represent, in part at least, an abnormal accumulation of fluids and the observations to be recorded below were undertaken to determine whether such a view might be tenable. Inasmuch as satisfactory procedures for the direct quantitative estimation of fluids in the structures were not immediately available, recourse to an indirect method seemed necessary. As a preliminary step, observations on the approximate water balance have been made whereby gross retention or release of fluid by the body as a whole might be measured during the course of therapy primarily dietetic in nature.

The recent review by Adolph on "Water Metabolism and Distribution in Tissues" has directed attention to the possibility that some of the dietetic and other measures used in the treatment of arthritic patients may have exerted among other effects a significant influence on the distribution of water in tissues.

Another matter requires mention at this point. One of the present authors, Pemberton has recently pointed out that the classical syndrome of arthritis may be regarded as characterized by imbalance of at least three of the major systems of the body, viz.; the circulatory, nervous and gastrointestinal. Several lines of observation, at the hands of a number of students of arthritis, justify this conclusion.^{3, 8, 13, 14, 16}

Clinical appreciation of some phase of this conception has long found expression in the views of Goldthwaite, Osgood, Swaim and their collaborators as to a probable "pooling" of blood in the arthritic, at least of the atrophic type. On the basis of this and other considerations these workers have advocated various postural attitudes and exercises which are accepted as having important clinical consequences. Sparks and Haden have also recently observed an increased blood volume in atrophic arthritis.¹⁷

The first mentioned, as well as the present writers, have been impressed with the importance of systemic rest in the therapy of arthritis and the present authors have reached a viewpoint in which rest in recumbency is regarded, not in the vague sense of avoidance of overactivity or fatigue but in a specific sense as contributory to changes in the gravitational influences, and are most easily appreciated in connection with the dynamics of the circulatory system, including particularly the capillary beds. They also have an equally important bearing upon the gastro-intestinal and, at least clinically, upon the nervous system as well. It may be remarked, parenthetically, that in the course of observations upon soldiers in service Pemberton and Foster, showed that arthritics, as compared with normals under similar conditions, present a very slight lag in the elimination of water, nitrogen and particularly salt when subjected to the so-called nephritic test meal.

In planning the experiments here reported, it was decided, therefore, to include also observations upon arthritics admitted to the hospital and at once given complete rest since in properly selected cases the subsidence of swelling referred to above can be early detected under these circumstances.

In view of the above considerations, studies were conducted upon the daily water exchange in thirty arthritics whereby an approximate estimate of the gain or loss of fluid by the body might be obtained. The subjects were selected from among the atrophic and hypertrophic patients, admitted to the arthritic services, most likely to exhibit the above mentioned reduction of soft tissue swelling. The state of the tissues with respect to extent of swelling, pain and limitation of motion was made on the basis of clinical observation, usually corroborated or checked by several persons. The method for calculating the water gain or loss is semi-quantitative.

Table 1
Outline of procedure for calcification of approximate water balance.
Daily water exchange.

INTAKE		OUTPUT	
Water as such		Urine	
Volume measured		Volume measured	
Water from food		Feces	
Servings weighed		Weight (gms.) X % water	
Composition calculated			
Preformed water		Skin and lung loss	
Water of oxidation		Estimate heat production	
Protein (gm.) X 0.413		H.P.* (cal.) X 0.6	
Fat (gms.) 1.07			
Carbohydrates (gms.) X 0.555			
Total			
"Approximate Water Balance" = Total Intake — Total Output			

*Heat production

As indicated in table 1 the gain or loss of water is obviously determined by subtracting the total water output from the total water intake. The water intake includes the water drunk as such and the water derived from the food. The latter factor represents the sum of water which is present in the servings and the water which is produced in the body by the combustion of the carbohydrate, fat and protein in any dietary mixture. The former fraction, viz., the water present as such in the food, is designated as preformed water and the latter, viz., the water produced by combustion within the body, as water of oxidation. The total water output includes the quantities eliminated through the kidney in the urine, through the bowel in the feces, through the skin and lungs in the form of sweat and water vapor.

The contributory factors constituting the total water loss are more or less evident, except perhaps, the indirectly calculated estimate of the skin and lung loss. Direct determination of the insensible losses were not made because of the fact that scales suitable for weighing patients with a sensitivity of a few grams were not available. In view of this fact, use was made of the empirical generalization of Benedict and Root that the insensible loss is a function of the heat production. The factor of 0.6 c.c. of water lost per calorie of heat production is taken from data presented by Adolph.

The fact that the activity of the patients under observation in the present series was relatively constant from day to day is believed to jus-

tify the use of this arbitrarily determined constant. It is recognized that the approximation of water calculated according to the above procedure falls short of the more complete and more nearly accurate estimate outlined by Wiley and Newburgh but as a practical expedient it appears to be adequate to reveal the contrasts upon which the present studies are based. In this general connection it is important to note that, with the deposition of one gram of protein or of carbohydrate in the tissues, approximately three grams of water are stored. The storage of one gram of fat is associated with the deposition of one tenth gram of water. During

Table 2
Daily water exchange in atrophic arthritis under conditions of rest in recumbency, slightly modified diet, and ward care.

Day of observation	P.	Diet F.	C.	Total Calories	Total H ₂ O Intake	Total H ₂ O Output	Balance
1	59	82	134	1506	1559	2150	—590
2	70	97	127	1661	2300	2810	—510
3	54	55	174	1406	1790	2460	—670
4	77	106	149	1860	2380	2398	— 18
5	69	77	136	1514	3055	2745	+310
6	88	106	169	1973	2170	2520	—350
7	60	79	243	2095	2205	2300	— 95
8	88	98	314	2470	2307	2540	—233
9	84	119	216	2271	2204	2170	+ 34
10	66	94	158	1744	2462	2665	—203
11	77	78	221	1943	2484	2260	+224
12	64	117	126	1811	2109	2780	—671
13	60	111	112	1690	1913	2055	—142

Estimated caloric requirement 1700 ca./24 hrs.

A progressive decrease in swelling, pain and limitation of motion occurred, the most rapid change taking place during the first few days.

starvation, the tissues are of necessity broken down to supply energy for metabolism and incidentally the water found by the substances catabolized is released. Under such circumstances there would be a net loss of water from the body. During periods of low caloric supply a negative water balance develops on the basis of the above premises. In view of these facts the food intake and the water balance are correlated with the clinical findings in the following cases.

In order to illustrate the general trend of the daily fluid exchange with respect to the clinical phenomenon of tissue swelling, data of a representative case of atrophic arthritis indicating an apparent systemic loss of fluid coincident with a decrease in tissue swelling, pain and limitation of motion are presented in table 2.

Of the several possible factors contributing to the above result the influence of the inadequate caloric intake voluntarily selected from the house diet by the subject must be considered. The following three cases illustrate the uncomplicated results of the reduced caloric intake. Each of the three patients in this group made significant advances during a preliminary period in the hospital, but at the time of the experimental period had reached a state of equilibrium with residual swelling.

In table 3 (Bkf) are shown the findings in such a stabilized case, in indicating that a sharp curtailment of calories results in a net loss of water from the body. This patient at the time of this observation had been a bed ridden invalid for twenty months and it is possible, therefore, to discount all essential influences referable to posture, the prone position, etc. The diet consisted of orange juice, milk for breakfast and lunch and a light mixed but balanced dinner. Coincident with the apparent water loss there is a reduction of tissue swelling. Like changes were observed in similar cases on correspondingly reduced food intakes.

Table 3
Daily water exchange in arthritic cases subjected to low caloric intake

Name	Time in bed before exper- imental period Mo.	P.	Diet F.	C.	Calories	Water Balance	Swelling Pain
Bkf.	20	47	81	121	1400	+200	Decreased
		23	37	93	800	-175	
		30	38	97	800	-175	
		44	103	98	1500	+200	
Fkln.	1	51	125	117	1800	-174	Decreased
		51	125	117	1800	- 58	
		17	16	71	500	-1050	
		17	16	71	500	-349	
		44	131	108	1800	+335	
		44	131	108	1800	-328	
Ce.	1	12	2	102	470	- 35	Reduced
		17	2	122	570	-591	
		21	11	148	675	-251	
		74	126	121	1910	-250	
		74	126	121	1910	+635	

Estimated calories required: Bkf. 1400; Fkln. 1600; Ce. 1900.

Table 3 (Fkln) shows the coincident reduction of swelling and net water loss under the influence of a low calorie, liquid diet consisting solely of orange juice and milk. It may be noted in passing, that a negative water balance occurs even in the presence of an unrestricted supply of water, under the conditions of a so-called fluid diet which provides a sub-maintenance total of calories. This is obviously referable to the fact that the tissues are called upon to supply the deficit of energy and incidentally yield the water with which the protein, fat and carbohydrate are combined.

The data of these two cases serve to emphasize the fact that dietetic measures may be utilized to induce further improvement in patients who have already been given the benefit of the sum of factors involved in a regimen including rest in recumbency. In each case sufficient time had elapsed before the dietetic measures were brought to bear, for a more or less stable equilibrium to be attained and it appears reasonable therefore, to attribute the change noted, to the reduced calorie intake uncomplicated by the physiological effects incident to postural changes. Further considerations bearing on this point will be mentioned later.

Table 3 (Ce) shows the effect in one patient of the vitamine-free diet, consisting of crackers, gruel, and coffee used by Pemberton, Peirce and

Bach in a series of cases recently reported. This diet is not only low in vitamins but is likewise calorically inadequate. A negative phase of water balance is coincident with the period of underfeeding. While this particular case, in which the most evident swelling consisted of an effusion in the knee, did not exhibit a distinct decrease in tissue swelling in the sense here understood, the deduction is unavoidable that similar systemic losses of water occurred in all of the patients included in the preceding series.¹⁴ A positive correlation of the observed rapid subsidence of tissue swelling with a negative water balance during the experimental diet periods presumably existed, therefore, in the series cited.¹⁴

The data presented suggest that the phenomenon of reduced tissue swelling is, under the conditions described, associated with nutritional factors involving a net loss of water from the body. The question may still be raised as to whether the subsidence of dietetic measures is due to, (1) a physiological variation of normal tissue substances and fluids; (2) a loss of pathological cellular tissue substance; (3) a loss of pathological surfeit of fluid. The first factor does not appear adequate in explanation because of the fact that the swelling tends to remain reduced in the post experimental periods following the physiological "pick-up" of the bulk of the water lost.

The data available at present are insufficient to provide an adequate basis for choice between the two last mentioned possibilities, although the evidence is suggestive of the existence of a pathological surfeit of extra cellular fluid. In further support of the view that something more than a normal physiological loss of water is involved, one experiment is cited in which an approximate estimate of the fluids released from the breakdown of normal tissues has been made.

Table 4 (Mrs. Sith) shows data on the fluid balance in a series of observations wherein technical errors seem to be at a minimum. While it is realized that the metabolic mixture derived from tissues must contain certain quantities of carbohydrate, data on the respiratory quotient are not at hand to indicate this ratio, and it is necessary to utilize the expedient approximation outlined above.

An approximation of the amount of water derived from the breakdown of cellular tissues has been made on the basis of the general premises indicated earlier as being operative during periods of submaintenance. The caloric difference between the diet and the estimated energy output has been assumed to be made up by tissue breakdown, with corresponding release of water. It is assumed that the negative nitrogen balance measures the protein loss. The amount of calories supplied by the tissue protein subtracted from the calorie deficit is taken as representing the fat burned. On the basis of the data so obtained the amount of water released by the breakdown of the protein and fat are calculated by considering that three grams of water are derived from one gram of protein and one tenth gram of water from each gram of fat. By adding to the sum of these quantities the amounts of water derived by oxidation, according to the method detailed in table 1, the total amount of water from the tissues is estimated. On the basis of such an estimate it appears that extracellular tissue water

contributed significantly to the net loss of water from the body under the conditions of a slightly submaintenance diet in a patient long previously stabilized with respect to the effect of posture.

If the phenomenon of reduction of swelling of tissues as here understood be related to systemic water loss, it might be expected that diets so devised as to be additionally dehydrating would induce the more marked clinical changes. Diets which approximate, in the percentage of the three food stuffs, the endogenous metabolic mixture utilized by the body consequent upon conditions of submaintenance might therefore be useful, in this regard, viz., diets relatively high in protein or high in fat as compared with the ordinary high carbohydrate supply. It might be noted here that the balanced diet recommended by one of the present authors usu-

Table 4

Daily water exchange in a patient who exhibited a subsidence of tissues on a submaintenance diet although stabilized with respect to effects of posture.

Day of ob- serva- tion	P.	Diet F.	C.	Estimated calo- ries	calorie output	Nitrogen Intake	Output	Water from break down				
								Tissue loss	of Tis- sues	Water Bal- ance	Water Bal- ance	
								P.	F.	(a.)	(b.)	
1	45	31	125	962	1350	7.2	10.3	19	35	97	-484	-387
2	44	49	89	980	1350	7.0	10.8	24	31	117	+331	+448
3	49	40	104	962	1350	7.8	11.2	21	34	112	-923	-811
4	49	37	85	869	1350	7.8	11.4	23	43	116	-542	-426
5	55	48	96	1036	1350	8.8	10.3	9	30	69	-531	-362
6	54	36	116	1008	1350	8.6	10.1	9	34	71	-190	-119

(a.) Water balance calculated according to procedure outlined before.

(b.) Water balance calculated according to scheme in text.

ally entails a reduction of the carbohydrate and a relative increase in the fat and protein as compared with the average dietary. From this point of view the experimental diets here discussed may be considered as extreme variants of the type of "arthritic" diet, most commonly used.

In order to illustrate the relationship of the protein and fat, several patients were placed on diets isocaloric with the preliminary diets but relatively increased in protein or fat.

Table 5 (Shck) shows typical findings in a subject, previously equilibrated with respect to posture, upon a diet relatively increased in protein. The diet was prepared with a minimum amount of salt, and the fluid intake was restricted. An apparent loss of water occurred with the observed reduction in tissue swelling. It should be noted in passing that this patient exhibited a subsidence of tissue swelling, of the type here discussed, despite the fact that she presented definite and advanced hypertrophic arthritis as evidenced by roentgenograms of the hands and knees. There was no cardiac decompensation.

It is to be further observed that two of the cases in the series here presented, showed unmistakable and uncomplicated evidence of hypertrophic arthritis. In some other cases, previously observed to respond in the same way to the nutritional principles involved, the type was equally definitely hypertrophic. The implication is therefore clear that both types

of the disease must be regarded as presenting, in some cases at least, the phenomenon of excess tissue fluids; and equally, that both types respond, to about the same extent, to the same therapeutic influences, in the sense above discussed.

Table 5 (Danr) shows findings in a case subjected to a ketogenic diet. This patient experienced a progressive decrease in swelling and pain during the period of observation. However, there seemed to be a slight acceleration in the rate of improvement during the period of increased water loss while on the ketogenic diet. The slight acceleration in rate of recovery in this and one other case (C. Sth) during a ketosis imposed by dietary means is not now to be considered a recommendation for the therapeutical application of such a diet. Further studies in this connection are pending.

Such observations as the above series affords, again indicate the necessity for taking into account the influence of dietetic factors which may be incidental to other therapeutic measures (Pemberton⁸). Further evidence is thus adduced that the early onset of objective improvements from surgical procedures, such as tonsillectomy, for example, is sometimes related to the nutritional state incidentally imposed rather than to the operation per se.

The influence is probably operative with all cases and may be conspicuous if the early clinical betterment, often experienced by patients as well as observed objectively, is not maintained.

During or following recovery from an operation which has not removed the cause of the arthritis, the patient usually returns to a fuller dietary, and swelling and pain may then gradually return. Instances of this are legion in the experience of every close observer of arthritis.

The favorable influence exerted on the arthritic by rest in recumbency has already been mentioned as contributory to the clinical improvement noted in patients subjected to hospital care. It has been further emphasized that the favorable effect of bed rest represents the resultant of many physiological and mechanical factors. The extent and nature of their inter-relationships, as they bear upon the arthritic problem, require more extended consideration.

The various major systems of the body, namely, the circulatory, nervous, gastro-intestinal and respiratory, are admittedly related to and inter-dependent upon, each other. A tendency still exists, however, in a clinical sense of the word, to regard these various systems as largely independent, for all practical purposes, and even autonomous. Although the influence of cardiac decompensation in producing gastric dysfunction is notorious, there is small appreciation of the fact that within the apparent limits of health close relationships exist. The reader need hardly be again reminded that the capillary beds in many of the tissues of the arthritic are accepted as being more or less shut down. The normal condition of the circulation in the capillary beds of the gastro-intestinal tract, is probably a factor, by definition, of the first importance, but the state of the capillary beds elsewhere in the body is almost equally important in that this determines in part the distribution of the blood in the gastro-intes-

tinal tract and in various tissues where its respiratory and other functions are exercised.

Among arthritic subjects, in whom anatomical displacements and dysfunctions of the gastro-intestinal tract are the rule as much as the exception, the relationships above referred to become even more significant. Inasmuch as the removal of gravitational influences, achieved by the assumption of the supine rather than the erect posture, profoundly alters conditions within the circulatory system, including conspicuously the capillary beds, it follows that these influences must presumably be reflected in the function of the various parts of the gastro-intestinal tract as a whole. To this consideration may be added the fact, as pointed out else-

Table 5
Approximate water exchange as influenced by qualitative character of diet.

Patient	Day	P.	Diet F.	C.	Calories (Intake)	Calories (Output) (Cal- culated)	Water Balance	Swelling Pain
Shck.	1	55	112	192	2000	1700	+398	Decreased
	2	46	74	84	1180	1700	(-50)	
	3	100	100	100(*)	1700	1700	-421	
	4	100	100	100(*)	1700	1700	-274	
	5	50	100	150	1700	1700	+ 52	
	6	55	95	125	1625	1700	-165	
Danr.	6	60	102	111	1774	1500	+244	Progressive decrease.
	7	60	102	114	1786	1500	-298	
	8	59	103	115	1735	1500	+162	
	9	53	163	15	1735	1500	-810	
	10	53	163	15	1735	1500	+268	
	11	53	163	15	1735	1500	-214	
	12	53	163	15	1735	1500	-250	
	13	63	119	115	1782	1500	+778	
	14	60	122	116	1799	1500	+478	
	15	58	112	107	1730	1500	+ 37	

*Low in salt, fluid intake restricted.

where, that such departures from normal within the gastro-intestinal tract as gastropptosis, enteroptosis and the like, with an attendant train of symptoms illustrated by hypochlorhydria, are equally benefitted by a position of recumbency in which gravitational influences, in the direction in which they have been previously operative, are modified or removed.

This brief recital of the influences which assumption of recumbency and betterment of the finer circulation, exert upon arthritis, and even upon normal subjects, will suffice to indicate, as the experiments cited show, that the prescription of recumbency and dietetics in arthritis constitute reciprocals which cannot wholly be divorced one from the other.

Thus, under conditions characterized by gravitational handicaps it is sometimes necessary among arthritics to reduce the load imposed by digestive and nutritional burdens to a minimum. Under conditions of restored gravitational equilibrium a greater nutritional and digestive burden may then often be assumed. After a certain departure from the normal is again reached, however, the nutritional and digestive burden must again be reduced even though the favorable influence of gravitational and postural

factors is at a maximum. The last possibility is illustrated by three cases in this series.

It might be expected that a condition, which for the moment may be designated as excess fluid in the tissues, would be open to influence from several directions and this is indeed the case.

It is perhaps hardly necessary to point out the therapeutic corollary to these considerations, viz.; that the arthritic subject must be given the benefit of the several measures and influences which achieve, or contribute to, betterment of the various disturbances of physiology presenting.

One phase of the above considerations relating to the effect of posture on the circulatory system may be considered in detail, viz.; the direction of the physiological transfer of fluid between the blood vessels and the tissue spaces following the assumption of various postures.

Table 6.
Relation of posture to the direction of fluid transfer, as shown by specific gravity of venous blood. Average of five cases

Time (min.)	Position	Sp. gr. venous blood plasma
0	Recumbent	1.026
20	Standing	1.028
40	Recumbent	1.026
60	Standing	1.028
80	Recumbent	1.026

Krogh and others¹ have shown that the assumption of the upright posture is associated with an increased flow of fluid from the capillaries to the tissues, whereas the direction of fluid transfer may take place in the opposite direction in changing to the recumbent position. In conformity with the above, the present authors have observed changes in the specific gravity of the venous blood of arthritics when standing and when lying down. Average data are shown in table 6.

From the above table there is evident transfer of fluid to the tissues from the blood on standing and an exchange in the reverse direction on lying down. It is suggested that this mechanism contributes to the reduction of swelling when patients are placed on a regimen which includes bed rest. Studies in the writers' laboratory indicate that a sufficiently refined technique for detecting possible differences between arthritics and normals in this respect is not yet available.

The suggestion is advanced, on the basis of the preliminary data here presented, that the phenomenon of tissue swelling in arthritis may be regarded as one expression of the factors operative to induce some other kinds of tissue swelling.

In the view that an abnormal fluid accumulation in the tissues contributes to the dynamic pathology of arthritis, several apparently diverse factors known to exert an influence on the symptoms may be conceived as having a common basis.

The accumulation of tissue fluid may contribute to the decreased variability of the heat regulating function of the skin noted by Pemberton and Wright. The cold clammy hands of arthritics may be related to the same factor. Analogously, meteorological changes which adversely influence

symptoms may be considered as acting through the inadequate range of potential adjustment of the tissues of arthritics to redistribute fluids readily. Similar considerations may apply to the decreased uptake of oxygen by the peripheral tissues¹¹ as well as to the delayed sugar removal.^{10, 20}

The slightly lowered basal metabolism encountered in about 33 per cent of arthritics^{4, 18} may depend in part upon an accumulation of inactive tissue fluid. The observation by Sparks and Haden¹⁶ of an increased plasma volume in atrophic arthritis further suggests that the relatively more fixed tissue-fluids are likewise increased. Many of the physical measures used therapeutically in the treatment of arthritis may achieve part of their benefit by the removal of fluid from tissues. Thus, local massage has been seen to increase urinary output²¹ perhaps by virtue of the increased lymph flow and circulation of blood which is induced. Heat acts to increase extrarenal losses and probably also acts to influence the local distribution of fluids.

Rest in recumbency is generally regarded as an effective means of bringing about a removal of fluid from the tissues in frank edema. While arthritics do not present derangements of the circulatory system to an extent which leads to frank edema they do occasionally present very persistent local edema. Pemberton and Peirce (unpublished data) have observed in the skin capillaries a stasis or sluggish flow which might be considered as contributory to accumulation of fluid in the skin.

The recognized relationship of the plasma protein to the fluid accumulation in nephrosis suggested the desirability of determining the relation of plasma proteins to the type of swelling observed in arthritis. Experiments in the writers' laboratory, however, have failed to reveal any gross deviation from normal values for total protein among arthritics. The albumin-globulin ratios likewise appear to be within normal limits. There is, however, an increase in fibrinogen which is, in general, parallel to the increase in sedimentation rate. While the data do not permit a precise evaluation, it is considered as possible that the increase of the protein fraction in plasma which alters the normal hydration of the red cells to the extent of increasing rouleaux formation and the sedimentation rate, may also function to influence the distribution of fluids in tissues.

The hypothesis is advanced that the swelling of tissues in arthritis is, in part at least, due to an excessive accumulation of fluids and further that dietetic and other measures which induce a reduction in swelling are associated with a net loss of fluid from the body.

Recognition of the probable participation of an abnormal distribution in the tissues, as part of the syndrome of arthritis carries with it no implication that this explains the whole syndrome, nor should the implication follow that dehydration by any and all means constitutes a "panacea" for arthritis. It is necessary only to point out that saline catharsis, intensive sweating and marked diuresis have been long and widely utilized, have been found to be of limited value only or even dangerous, and, by general consent, do not as such constitute the "way out" for arthritics. Rather should emphasis be placed upon measures or influences which op-

erate in a more sustained way, without abrupt dislocation of function and without the imposition of further burdens.

Although clinical use of dietetics has had large substantiation at many hands and although laboratory studies of several kinds have adduced suggestive support, further precise data have been desirable. It is perhaps desirable, therefore, to point out that the considerations advanced in the present text carry further justification for the use of dietetics in the problem of arthritis. This is not to say, however, that the mechanism concerned in the influence of dietetics, above discussed, constitutes the only means by which dietetics may exert an influence in arthritis. The experimental diets discussed are not to be confused with the optimal type of diet often necessary in the conduction of therapy over long periods of time. Furthermore, the reader is hereby cautioned that the use of dietetics in the way above described is not to be interpreted as a "blanket" form of therapy.

The authors are indebted to Dr. Theodore F. Bach for assistance in clinical details and to Miss M. Robinson for supplying data on the weights and composition of the foods consumed by the patients.

SUMMARY

Attention is directed to the fact that convalescence from arthritis is frequently characterized by a reduction of soft tissue swelling, particularly evident, though rarely conspicuous, in the hands and concurrent with a diminution of pain and increasing range of joint motion.

In a short series of selected cases, approximate water balance estimations have indicated that a net loss of water from the body occurs *pari-passu* with a subsidence of swelling of tissues, pain, and limitation of motion.

The hypothesis is advanced that disturbances of water distribution in tissues constitute significant factors in the dynamic pathology of the rheumatoid syndrome.

An attempt to evaluate the rôle of dietetic and other factors in the above series of events has been made by studying the several separate phases contributing to the net result. The administration of several types of low calorie diets has been shown to be associated with a net loss of water and with clinical improvement.

Dehydrating diets, adequate in calories, high in protein, low in fluid and high in fat induced a net loss of water from arthritics with clinical evidence of improvement and the suggestion is made that the relative increase of fat and protein established on low calorie diets exerts a significant influence in the striking clinical results frequently achieved.

Rest in recumbency is considered as acting, in part, by favorably influencing a shift of fluid from the tissues to the blood and lymph channels.

Many seemingly unrelated factors which influence arthritis favorably when used within proper limits, such as, dietetics, rest in recumbency, heat and massage may be reasonably conceived as acting in part by favoring fluid removal from tissue.

Attention is directed to the fact that a negative water balance con-

tributes to recovery from both atrophic and hypertrophic arthritis. This fact may be considered as suggestive that both types of arthritis arise, in part, from similar or comparable premises; and, further, that rigid restriction of most therapeutic measures, especially those here mentioned, to one type alone, is unwarranted.

The relationships here pointed out are not to be considered as implying that dehydration measures constitute alone a therapeutic escape from arthritis.

Vigorous sweating, purgation or diuresis have long since been evaluated, as of limited value only, and even dangerous. So far as changes in the distribution of tissue fluids in arthritis may be desirable, they should be achieved by the more sustained and "physiological" influences and measures referred to in the text.

Further justification is afforded for the controlled use of dietetics in the treatment of arthritics. The reader is again cautioned as to the dangers involved in uncritical employment of this agency.

DISCUSSION

DR. A. ALMON FLETCHER, Toronto: The symptoms of an arthritic patient may change abruptly following a number of events: atmospheric change, removal of foci, use of vaccines, and so forth. A patient will experience marked morning stiffness and pain with increase of swelling noted on arising in the morning. A few hours later he is much better. A varying edema of tissues has been considered a possible cause of morning stiffness. It is interesting to learn that Drs. Pemberton and Scull have noted abrupt improvement with shifts in water balance and metabolism under the influence of low caloric diets. However we must be careful in our application of such observations as physicians in general are apt to resort to one favorite method of treatment and may be lead to use sub-maintenance diet to the exclusion of other useful therapeutic measures. Patients with arthritis are suffering with a chronic disease due to a variety of factors. All measures calculated to overcome these various factors must be used and we must combat the sentiment of patients and physicians to use one measure, such as a diet to the exclusion of others, for diets alone may be ineffective.

DR. F. J. SLADEN, Detroit: Fearful of the possible harm that might result from the use of starvation periods such as advocated by Dr. Pemberton for use as a preliminary measure to further treatment by diet of patients with severe arthritis, I have considered them justified only in relative emergencies, when nothing else has helped. Although I have never understood why, I have had very satisfactory results when I have tried them. I am interested in the explanation suggested now by Drs. Scull and Pemberton. However, I believe there must be a more profound factor at work which we haven't yet discovered.

DR. PEMBERTON: I welcome Dr. Sladen's comment that care must be taken in prescribing sub-maintenance diets in these cases. There are definite dangers inherent in undernutrition as there are in many of the measures used for arthritis. Our laboratory work is of an academic nature chiefly—an attempt to study some of the physiological factors underlying the production and reduction of swelling. I know of no way to explain this tissue swelling. It may be an inflammatory exudate but it is difficult for me to interpret it as such.

DR. WALTER BAUER, Boston: From the data presented, one is not justified in drawing any final conclusions concerning the water balance. Not until one actually determines the total acid-base metabolism and insensible perspiration throughout the experimental period can one state with certainty whether there has been an actual loss or gain of water.

DR. SCULL: These patients were subjected to a fairly constant regimen, so that there was little likelihood of increasing or changing the sensible loss from day to day. We, therefore, considered that it represented a constant. We included observations on acid-base balance. We admit that these experiments are somewhat preliminary in nature.

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FOCAL INFECTION AND ARTHRITIS A STATISTICAL STUDY

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Almost one hundred and twenty years have passed since Benjamin Rush emphasized the effect of dental disease upon generalized arthritis, and more than twenty years have passed since Billings and Rosenow forcefully directed the attention of the medical profession to the problem of focal infection; nevertheless we find ourselves today still in the midst of an active controversy in which such a relationship between local and systemic disease is challenged, both in principle and in fact.

Considering the high incidence of focal disease, on the one hand, and the great fluctuations in the usual course of systemic disease on the other, it is not strange that this question is a most difficult one to settle.

THE MODE AND ROUTE OF INFECTION

Does a state of bacteremia exist, maintained by a focus of infection? If so, what is the incidence of positive blood cultures? Forkner, Shands and Poston found a high incidence (60 per cent) of bacteria in the synovia, or in the lymph glands, and others such as Cecil, Nicholls and Stainsby found a high incidence (62.3 per cent) in the blood. They believe that chronic infectious arthritis is a streptococcus infection caused by a biologically specific strain. On the other hand, Dawson, Olmsted and Boots found streptococci in only 3.7 per cent, and Richards in only 7 per cent of blood cultures of arthritic subjects. Furthermore Lichtman and Gross, in a series of 5,000 consecutive cases, found from 5 to 15 per cent positive blood cultures in non-arthritic cases. Therefore it seems doubtful whether the presence of streptococci in the blood or joints of arthritics can be demonstrated in a percentage materially higher than in blood cultures in non-arthritic cases. Of course the discrepancies in these findings do not overthrow the conception of chronic infectious arthritis as a systemic disease. It is merely a question as to whether the joint manifestations are actually metastatic, or are produced by some toxic agency upon the joint.

THE QUESTION OF ELECTIVE LOCALIZATION

Rosenow's theory of elective localization, based upon the specific nature of bacteria, has not been sufficiently proved in man. It would seem that the prevalent localizations are those which cause alterations in the circulation, and thereby affect the nutrition of the cell tissues, especially of the epithelium and of the capillaries (Holman). All in all, the specificity of the bacteria has not been proved, and it is much more likely that the determining factors may be found in the tissues of the host, (they are much more variable and much more important). Kolmer believes that the idea of tissue affinity on the part of the invading organism has been greatly

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over-emphasized. Rather the question is, why are some people more susceptible to secondary focal infections than are others? What are the agencies which determine why some people are more prone to secondary focal infection? These questions cannot be answered except from the point of view of individual propensities; constitutional, hereditary, or acquired.

Because of the individual's hereditary tendency to arthritis, the incidence of foci assumes a greater significance. Infection from a focus which is harmless in the non-arthritic becomes more serious in the hereditary arthritic subject. Therefore the evaluation of the focus, it seems to me, should be considered in the light of a combination of focus and arthritic diathesis, rather than from the point of view of statistical numbers of incidence of foci alone.

INCIDENCE

Total.—The total number of cases of non-specific arthritis in our series is 4,339, of which 3,004 were of type 1 (atrophic), 1,335 of type 2 (hypertrophic) and 15 of the mixed type. The numerous cases in type 2 which become later superimposed on type 1 are recorded under type 1. The incidence of foci established in type 1 is 522, or about 17 per cent, and 240 in type 2, or about 17.7 per cent. However, because of the many ambulatory cases in which thorough search for foci could not be made, we believe these figures are much too low (table 1).

The most common site of focal infection.—The most common sites of infection are as follows: tonsils, teeth, sinuses, gastro-intestinal tract, prostate gland and adnexa. The incidence of these sites of infection in arthritic clinics must be compared with the general incidence in non-arthritic diseases.

The tonsils. After the first year of life there are no tonsils in which pathological changes cannot be found (Caylor and Dick). A hemolytic streptococcus was encountered in 90 per cent (Julianelle). Keilty, in a study of 388 cases, reported sixteen different types and fifty-three combinations of organisms in the tonsils. Miltner and Kulowski, in 100 cases of chronic atrophic arthritis observed in our clinic, found the incidence of the tonsillar focus alone in 42 per cent (24 per cent of which were in patients under sixteen years, and 18 per cent in patients over sixteen). In hypertrophic arthritis it was 22 per cent.

Our statistics are as follows: among 522 cases of atrophic arthritis (type 1) in which foci were established, tonsils alone were found involved in 161 cases (30 per cent), in combination with sinuses in 136 cases (25 per cent), total 55 per cent (table 1). Among 240 cases of hypertrophic arthritis (type 2) in which foci were established, the tonsils alone were involved in 18, in combination with teeth in 15, with sinuses in 80, and with teeth and sinuses in 41, making a total of 154 or 65 per cent (table 1).

Teeth. Pyorrhea and suppurations in the root canal are the two most important conditions. Mutch found 52 per cent of patients with chronic arthritis had dental sepsis, which is in keeping with the high incidence of sepsis in the throat. However, in our series described by Miltner and Kulowski, the incidence of established dental disease is only 22 per cent for the atrophic type and 43 per cent for the hypertrophic arthritis. Arnett

and Ennis in their routine medical and dental examinations, including dental roentgenograms, found dental caries in 83 per cent of the cases, and chronic rarefying osteitis in 19.8 per cent.

Distant foci are harder to evaluate than dental foci. W. A. Price, studying dental infection from the viewpoint of the chemical changes in the blood, distinguishes three kinds of relationships. In cases of dental infection in the non-rheumatic and non-susceptible group there is a large zone of rarefaction which constitutes a barrier between the teeth and the host. In a second group, with a more or less condensing osteitis about the zone of rarefaction, the barrier is not sufficient, the organism and toxin

Table 1
Incidence of foci established, absolute relative incidence of foci—all ages

Site	Type 1			Type 2		
	Number	Per cent of all foci	Total	Number	Per cent of all foci	Total
Tonsils	161	30.)	297 = 55 per cent	18	7.5)	154 = 64 per cent
Tonsils and sinuses	136	25.)		80	33.)	
Tonsils and teeth				15	6.2)	
Tonsils, teeth and sinuses				41	17.)	
Teeth	71	13.5)	86 = 16.5 per cent	40	16.7)	55 = 23 per cent
Teeth and sinuses	15	2.9)		15	6.2)	
Sinuses	92	17.8)	243 = 45.7 per cent	15	6.2)	136 = 56.7 per cent
Sinuses and teeth	15	2.9)				
Sinuses and tonsils	136	25.)		80	33.)	
Sinuses, teeth and tonsils				41	17.)	
Gastro-intestinal (incl. biliary)	7	1.3)	8 = 1.5 per cent	15	6.2)	17 = 7 per cent
	1	0.2)		2	0.8)	
Genito-urinary:						
Prostate (m)	8	1.5)	30 = 5.7 per cent	5	2.0)	13 = 5.3 per cent
Adnexa (f)	22	4.7)		8	3.3)	
TOTAL	522			240		

*Type 1, 522 : 3004 = 17 per cent; Type 2, 240 : 1350 = 18 per cent

are not destroyed, and these patients have an acquired susceptibility which is checked by bone reaction. In the third group there is little evidence of reaction about the teeth or the root apex; toxic infection appears to be invading the patient. The teeth are not sore, they are easy to extract, and these Price places in the class of inherited susceptibility. In type 1 of our series, dental foci alone were found in 71 cases, in connection with sinuses in 15 cases, making a total of 86 cases, or 16.5 per cent. In type 2 dental foci were established in 40 cases, and in combination with sinuses in 15 cases, making a total of 55 cases or 23 per cent.

The sinuses. Attention has been called by Byfield and Jeans to the high incidence of sinus infection in children. Secondary infection coming from sinuses are blood borne, namely either a bacteremia or a toxemia from the absorption of a highly virulent toxin. However, secondary infec-

tion does not seem to result as frequently from an acute disorder as would be expected from the virulence and the amount of pathological changes, according to Lawson.

In the earlier series, reported by Miltner and Kulowski, the paranasal sinuses were involved in 23 per cent of the atrophic type, and 19 per cent in the hypertrophic type. Chronic tonsillar disease of long standing almost invariably produces chronic sinusitis. In our series of cases of atrophic arthritis (type 1) sinuses alone were involved in 92 cases, or 17.8 per cent; in connection with teeth in 15 cases, or 2.9 per cent; in connection with tonsils in 136 cases, or 45.7 per cent. In our cases of hypertrophic arthritis (type 2), sinuses alone were involved in 15 cases, or 6.2 per cent; in conjunction with tonsils in 80 cases, or 33 per cent; in connection with teeth and tonsils in 41 cases, or 17 per cent, total 136 cases, or 56 per cent.

Table 2
General statistics on eradication of foci

	Total Number a	Total Number foci estab- lished b	Per cent—c established total a	Total foci eradicated c	Per cent—c established eradicated b	Total positive results d	Per cent—d eradicated resp. c
Type 1	3004	522	17	254	48.6	90	35
Type 2	1350	240	18	135	56.	27	20
Total 3	4354	762	17.5	389	51.	117	30

In our series the incidence of sinus disease in arthritis may be noted (table 1).

The gastro-intestinal tract. It should be considered first that bacteria do not readily invade healthy intestinal mucosa. Active predisposing elements, such as intestinal irritation or diarrhea, and auto-intoxication, produced by constipation, facilitate penetration of the toxin into the system. The high incidence of streptococcus in the intestines has been pointed out by Miltner and Kulowski; it occurs in 14 per cent in cases of the atrophic type, and in 16 per cent in cases of the hypertrophic type. The gastro-intestinal tract, particularly the colon, plays a large part in the absorption of toxin. The significance of redundancy of the colon and the incompetence of the ileo-cecal valve have been repeatedly discussed. However, if one considers the high incidence of such redundancy in non-arthritic cases (Haft), the importance of this condition becomes less. The biliary tract also is often suspected of harboring infection in cases of arthritis; Hartung and Steinbrocker investigated this question in 200 cases of gallbladder infection in patients with arthritis, and found that of 30 suspected cases who were subjected to cholecystography, 25 had normal gallbladder function, and only five were considered infected. Four more gave additional evidence of gallbladder infection. Of these 9 cases, 6 had osteo-arthritis, only three being of the infective type. Therefore since the incidence of gallbladder disease in arthritis seems to be only 4.5 per cent,

as against 5 per cent in disease in general (as shown by a report from The Mayo Clinic), Hartung and Steinbrocker conclude that the incidence of gallbladder infection is as high in patients of the non-arthritic group as it is in the arthritic group. Our own report of gastro-intestinal disease is as follows: In atrophic arthritis (type 1) 7 patients had disease of the gastro-intestinal tract and 1 patient had a biliary infection; total 8 cases, or 1.5 per cent. In hypertrophic arthritis (type 2) 15 patients had disease of the gastro-intestinal tract or 6.2 per cent, and 2 patients had biliary infection, or 0.8 per cent (table 1).

The prostate gland. Waller described the incidence and relationship of the prostate gland as a secondary or primary focus in arthritis. Aside from the true gonorrheal infections which are not considered in this series, the incidence of prostatitis as a focus is very low. Miltner and Kulowski in our series, found the genito-urinary tract a focus in 5 per cent of cases of the atrophic type and in 14 per cent of the hypertrophic type. The latter includes both gonorrheal infections and hypertrophy of the prostate gland, which are not uncommon among men of the age at which arthritis occurs. In our series (table 1) we found in type 1 arthritis, involvement of the prostate gland in 8 cases, or 4.5 per cent; and of the adnexa, in 22 cases, or 4.5 per cent; total 30 cases, or 5.7 per cent. In type 2 (hypertrophic arthritis) the prostate gland was involved in 5 cases, or 2 per cent and the adnexa in 8 cases or 3.3 per cent; total 13 cases or 5.3 per cent (table 1).

THE SYNOVIA

The question of the arthritic joint fluid as a source of infection was brought up first by Swett, who studied the curative merits of synovectomy. In a former paper (1925) I reported 20 cases of synovectomy, which showed a definite relationship between the synovia and infection, but found furthermore that the effect of synovectomy is chiefly mechanical. Ellis Jones, in 1923, selected 12 of 300 cases of chronic arthritis of the knee joint for synovectomy. He believed that it had a distinct value, but the question whether or not it is due to the elimination of focus or the elimination of a mechanical element is still undecided. In our series we found only two cases in arthritis of type 2, or 0.8 per cent, in which the prompt general improvement following synovectomy justified the assumption of a synovial focus.

THE EFFECT OF REMOVAL OF FOCI UPON ARTHRITIS

The definition of a focus of infection implies that there exists a circumscribed focal lesion, that the lesion has a bacterial nature capable of dissemination, and that a systemic condition has resulted from a dissemination of the focus.

As far as the relation of the focus of infection to arthritis is concerned it seems to me that the proof demands both quantitative and qualitative evidence. The quantitative factors were discussed when I cited and compared the incidence of focal infection in both arthritic and non-arthritic individuals.

The qualitative evidence rests upon the intensity of reaction and promptness of response of the arthritis to the removal or treatment of the supposed focus. Cure of a patient, after removal of foci or after treat-

ment, is generally considered convincing evidence that the focus was the seat of infection. This evidence, however, is not entirely conclusive, because the cure may be due to the general bodily improvement that results from the removal of a focus which is causing lowered systemic resistance.

Table 2			
Type 1:	Age group 0-10	Per cent	
	Tonsils	60	combined age group response all foci 9 of 23
	Sinuses	36	
	Combined	20	
	Age group 10-20		
	Tonsils	35	combined age group response all foci 19 of 53
	Sinuses	10	
	Combined	60	
	Age group 20-40		
	Tonsils	43	combined age group response all foci 42 of 118
	Teeth	36	
	Sinuses	26	
	Combined	35	
	Age group 40 and over		
	Tonsils	36	combined age group response all foci 20 of 60
	Teeth	31.8	
	Sinuses	25	
	Combined	43	

In type 1, the total response at all ages and for all foci was 90 of 254 or 35 per cent.

The exacerbation of the local condition which follows the removal of the primary focus may likewise be considered strong presumptive evidence of the relationship between the primary focus and secondary infection (Kolmer).

Table 3
Immediate responses to eradication
according to age groups and site of focus in percentages*

Age groups	Type 1				Type 2	
	0-10	10-20	20-40	40 and over	all age groups	all ages Per cent
Tonsils	60 per cent	35 per cent	43 per cent	36.0 per cent		36.0
Sinuses	36 per cent	10 per cent	36 per cent	25.0 per cent		10.0
Combined	20 per cent	60 per cent	35 per cent	43.0 per cent		
Teeth				31.8 per cent		6.5
Tonsils and teeth						0.9
Tonsils and sinuses						32.0
Tonsils, teeth and sinuses						33.0
Gastro-intestinal						27.0
Prostate, bladder						33.0
Adnexa						0.0
All foci, per cent	39	36	36	37	35	20

*Total number of cases 90 = 35 per cent of all eradications

In our series of cases we have considered, in the group representing evidence of relationship between foci and arthritis, only those in which either cure or a decided improvement followed the removal of the focus in sufficiently short time to carry conviction.

RESPONSE FOLLOWING REMOVAL OF FOCI AND TREATMENT ACCORDING

TO AGE AND TYPE

In a series reported by Miltner and Kulowski, we found in atrophic arthritis (type 1) after eradication of the primary focus of infection in patients up to sixteen years of age, there was apparent cure in 73 per cent, and marked improvement in 16 per cent. In those patients over sixteen years of age, apparent cure was found in 15 per cent, and marked

Table 4
Analysis of fifty-one positive responses to focal removal
(Type 1)

	Onset	Course				Age Groups				Duration	Re- sponse to focal removal	Re- sponse to other treatment	Ob- servation							
		Acute and sub-acute	Chronic and gradual	Progressive	Intermittent	—10	—20	—40	40+	Less than 2 years	More than 2 years	Immediate	Not immediate	Yes	No	Not recorded	Less than 1 year	More than 1 year	More than 3 years	Total number type 1
Tonsils		7	15	21	2	7	7	7	14	7	15	6	2	2	17	12	6	3	21	
Teeth		2	5	6	1	1	5	2	5	3	5	3	2		5	4	3	1	8	
Sinuses		2	7	9	2		3	4	4	5	3	6	1		8	3	4	2	9	
Tonsils and sinuses		3	7	10	1	4	3	2	5	5	7	3	2	2	7	2	4	4	10	
Tonsils and teeth		1	2	2		1	1	1	1	2	3		1		2	1		2	3	
All foci		15	36	48	3	3	13	19	16	29	22	33	18	8	4	39	22	17	12	51
		51		51		51		51		51		51		51		51				

improvement in 58 per cent. In hypertrophic arthritis (type 2) which included older people, we found apparent cure in none, marked improvement in 9 per cent, and no improvement in 91 per cent of all cases. Our own series shows the following general features (table 2): Type 1, total number of foci established 522 or 17 per cent; total foci eradicated 8.4 per cent; positive responses upon eradication of established foci were found in 90 cases of 254, or 35 per cent. In type 2, total number of foci established 240, of a total number of 1350 patients, or 18 per cent; total foci eradicated 11.2 per cent; positive responses upon eradication of established foci were 20 per cent, 27 cases of 135.

ANALYSIS OF THE GROUP OF CASES IN WHICH THERE WAS DEFINITE

IMPROVEMENT AFTER REMOVAL OF FOCUS

In a former series (Miltner and Kulowski) it was found that the foci among children were more readily recognized, and were less widespread and diversified. The result following eradication of foci in this

series was at least 25 per cent better than in a similar group in which there was no attention given to foci of infection.

We found, further, that the eradication of foci is of great importance among children, since the results are nearly always strikingly positive; in adults, the beneficial results depend upon the age of the patient and the duration of the disease. In determining the effect, the cessation of pain and correction of deformities, and general improvement are the prime factors. The eradication of a focus in the atrophic type in general revealed a definite, not inconsiderable improvement. Attention to foci in the hypertrophic type, on the whole, does not materially influence the result.

The responses according to ages and site of focus are classified in tables 2 and 3.

Table 5
Analysis of seventeen positive responses to focal removal
(Type 2)

	Onset		Course		Age group		Duration		Re- sponse to focal removal		Re- sponse to other treatment		Observation				
	Sudden	Gradual	Progressive	Intermittent	Less than 40 years	More than 40 years	Less than 2 years	More than 2 years	Immediate	Not Immediate	Yes	No	Not recorded	Less than 1 year	More than 1 year	More than 3 years	Total type 2
Tonsils		2	1	1		2	1	1	1	1		1	1	1		1	2
Teeth	2	2	4			4	2	2	3	1	1		3	4			4
Sinuses	1		1			1		1		1	1				1		1
Tonsils and sinuses	2	2	3	1	1	3	3	1	3	1	1		3	2	2		3
Tonsils and teeth		3	2	1	1	2		3	2	1	1		2	3			3
Tonsils, teeth and sinuses		1	1		1		1			1			1	1			1
Synovia	1		1		1		1			1		1		1			1
Prostate		1	1			1	1			1		1			1		1
All foci	6	11	14	3	4	13	8	9	9	8	4	3	10	12	4	1	17
	17		17		17		17		17		17		17				

We next selected all cases in which improvement was striking following eradication of foci, both subjectively and objectively. This group includes 51 cases of atrophic arthritis (type 1) and 17 cases of hypertrophic (type 2), with both immediate and delayed responses. In table 4 it may be noted that the onset was acute and subacute in 15 cases; chronic in 36, the type was progressive in 48 cases and intermittent in 3. Age group 0-10, three; 10-20, thirteen; 20-40, nineteen; over 40, sixteen. Duration of arthritis: less than 2 years, nineteen; more, twenty-two. Responses: immediate, thirty-three; delayed, eighteen. Responses to other previous treatment: yes, eight; no, four; not recorded, thirty-nine. Observation

time: less than one year, twenty-two; more than one year, seventeen; more than three years, twelve.

In table 5 may be noted the analysis of the seventeen definite responses in arthritis of type 2. Onset (all foci): post-traumatic and acute, six gradual, eleven. Course: progressive, fourteen; intermittent, three. Age: under forty, four; over forty, thirteen. Duration of arthritis: less than two years, eight; more, nine. Response: immediate, nine; delayed, eight; Response to other treatment: yes, four; no, three; not recorded, ten. Observation: less than one year, twelve; more than one year, four; more than three years, one.

Finally we eliminated from this group of 51 cases of type 1 in which responses were positive, and from the seventeen of type 2, all cases in which recurrences of arthritic symptoms took place during the time of observation; 12 cases, in which the arthritis was of type 1 and six cases in which it was of type 2. Causes of recurrences were either a recurrent focus or appearance of other foci (table 6). This leaves an ultimate

Table 6
Positive response to eradication of foci
Recurrences

	Type 1							Type 2						
	Course	Duration		Cause of		Total		Course	Duration		Cause of		Total	
	Prog.	Intermittent	Less than 1 year	More than 1 year	Recurrence Foci	Other Foci		Prog.	Intermittent	Less than 1 year	More than 1 year	Recurrence Foci	Other Foci	Total 1 and 2
Tonsils	3	1	3	1	3	1	4	1		1			1	5
Teeth								1		1			1	1
Sinuses	3		1	2	2	1	3							3
Tonsils and sinuses	3		3		2	1	3	2		2			2	5
Teeth and tonsils	1	1	1	1	2		2							2
Tonsils, teeth and sinuses														
Synovia								1		1		1		1
Prostate								1			1	1		1
All foci	10	2	8	4	9	3	12	6		5	1	2	4	18
		12		12		12				6		6		

group of thirty-nine cases of type 1 and eleven cases of type 2, total 50 cases, of which it can be stated that upon eradication of foci, there was not only decided improvement of the arthritic condition, but that this improvement was uniformly maintained throughout the entire period of observation. The details of this last group, arranged according to focus and time of observation are given in table 7.

COMMENT AND CONCLUSIONS

The response in 15 per cent of cases of arthritis of type 1, and 8.1 per cent in cases of arthritis of type 2, approach, we believe, the lower

limit of frequency, of definite and lasting responses to removal of foci. The number of observations of less than a year was partly offset by the elimination of cases in which there was immediate response but no post-operative observation, of which a number of patients undoubtedly would have progressed to uninterrupted improvement. Also among the cases in which there were recurrences, which were likewise eliminated, were cases in which recurrences did not take place for two years or more.

Table 7
Cases of marked, definite and uninterrupted improvement or cure after eradication

	Type 1, Observation (years)					Type 2, Observation (years)					Total 1 and 2
	-1	1-2	2-3	3+	Total	-1	1-2	2-3	3+	Total	
Tonsils	14	4	1	1	20	1				1	21
Teeth	1	1	1	1	4	1	1			2	6
Sinuses	2	3		1	6	1	1			2	8
Tonsils and sinuses		4		2	6	3				3	9
Tonsils and teeth	2	1			3	2				2	5
Joints (synovial)								1		1	1
All foci	19	13	2	5	39	8	2	1		11	50

Type 1, 39 cases = 15 per cent; type 2, 11 cases = 8.1 per cent.

The 117 definite responses (90, type 1 and 27, type 2) which include the group of 50, with definite and lasting improvement should be considered as the upper limit of frequency of positive responses to eradication of foci. They represent 35 per cent in cases of type 1 and 20 per cent in those of type 2 in which the foci were eradicated.

It is safe to assume that between these two values, namely 35 per cent, and 15 per cent of type 1, and 20 per cent and 8.1 per cent of type 2, lie the percentages of all cases which represent the real practical benefit resulting from the eradication of foci.

This investigation seems to indicate that the search for foci of infection in the upper respiratory tract and in other systems of the body is justified in the routine examination of all cases and types of arthritis.

THE TREATMENT OF CHRONIC RHEUMATOID ARTHRITIS WITH STREPTOCOCCAL VACCINE, ON THE BASIS OF SKIN SENSITIVITY

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The relation of streptococci and streptococcal infection to chronic rheumatoid arthritis remains in an uncertain and far from established position in spite of the many diligent investigations pursued during the past decade. Not only do students of the disease differ about the interpretation of experimental results but the results themselves lack uniformity. If a relationship exists, it might exist in one of three ways: (1) The joint lesions may be the result of the localization of streptococci circulating in the blood stream; (2) the joint lesions may be due to toxins liberated from some focus of streptococcal infection elsewhere in the body; or (3) the joint reactions may be allergic in nature and represent hypersensitivity of the joint tissues to streptococci, resulting from low grade infections or from the persistence of foci of infection in the body. If the first relation obtains, then the nature of the joint change and the method of its production are easily understood, for we are dealing with a metastatic infection. If the second, then a high degree of specificity is implied. If the third, then an equally high degree of specificity exists, or else we must assume with Wetherby and Clawson that there is a species rather than a strain specificity. If we regard the joint changes as allergic it is at times difficult to explain just how the contact of antigen with antibody in the allergic joint comes about.

The announcement by Cecil, Nicholls and Stainsby in 1929 that they had isolated an atypical hemolytic streptococcus from the blood stream and joints of over two-thirds of their patients with chronic rheumatoid arthritis immediately aroused great interest. Not only was the percentage of their positive cultures far larger than that obtained by previous investigators but the report was particularly noteworthy since the organism isolated was hemolytic. The ability of their "typical strain" to hemolyze blood was at variance with the cultural characteristics of the organisms previously isolated by Moon and Edwards, Richards, Hadjopoulos and Burbank and others. These investigators had reported finding a *Streptococcus viridans* in blood cultures, although in only a small number of cases. Cecil, Nicholls and Stainsby were able by the intravenous injection into rabbits of their "typical" hemolytic streptococcus to produce an arthritis analogous to rheumatoid arthritis in human beings, without associated visceral lesions, and to recover the organism from the blood stream and joints of their inoculated animals.

The results of Cecil and his coworkers have been confirmed by some investigators, denied by others. For instance, Klugh was able to isolate

a streptococcus in an even larger percentage of cases, namely 72 per cent, Gray and Gowen in 58 per cent, and Wetherby and Clawson in 50 per cent. In these reports the organism is classified as a *Streptococcus viridans*. On the other hand, Dawson, Olmstead and Boots were able to recover a streptococcus from only 2.5 per cent of their cases, and Nye and Waxelbaum obtained no streptococci in any of their cases of either acute or chronic infectious arthritis. Lichtman and Gross grew streptococci from only 9 per cent of their series and considered this percentage no greater than that of the "transient streptococcemias found in the routine blood culture work of a general hospital."

Although the lack of uniformity in the results obtained from blood cultures is striking, the presence of serum agglutinins for hemolytic streptococci in a very large percentage of cases of rheumatoid arthritis has been reported by numerous observers. Dawson, Olmstead and Boots found that 67 per cent of 157 cases possessed this property in their sera to a dilution varying from 1-20 to 1-2, 560 or higher. Nicholls and Stainsby found streptococcal agglutinins present in the sera of practically all patients with chronic infectious arthritis when their "typical strains" were used. Keefer, Myers and Oppel found that 54.5 per cent of their patients with rheumatoid arthritis showed positive blood serum agglutinins for the four strains of hemolytic streptococci used.

It has also been reported that patients suffering from rheumatoid arthritis show positive skin reactions to killed streptococci and their fractions in a larger percentage than do healthy persons or those suffering from some other disease. In approaching the subject from another angle, Birkhaug found that 47 per cent of sixty-nine cases of chronic arthritis showed marked skin reactions to both non-hemolytic and hemolytic streptococci. Myers, Keefer and Oppel obtained positive reactions to the nucleoprotein of a strain of *Streptococcus scarlatinae* in 70 per cent of their cases of rheumatoid arthritis, whereas 44 per cent of their control series gave positive reactions. In 32 per cent of the cases of rheumatoid arthritis the reaction was marked, whereas it was marked in but 12 per cent of the controls. Wetherby and Clawson found that 91.8 per cent of their cases of chronic arthritis gave positive reactions when tested intradermally with a *Streptococcus viridans* obtained from the blood of a patient with acute rheumatic fever. A positive reaction was obtained in only 49.6 per cent of their controls. They felt that the positive skin test probably indicated hypersensitiveness to the strain of streptococcus used and that the percentage of positive reactions was significantly higher in chronic arthritis patients than in a series of controls.

BLOOD CULTURES

The recovery of streptococci from the blood stream and joints of such a large percentage of cases of rheumatoid arthritis is a matter of great importance. If the observations are confirmed, then we must regard the arthritis as metastatic. At the Johns Hopkins Hospital we have been unable to duplicate the results of Cecil, Nicholls and Stainsby. Ninety-four blood cultures were made in ninety-one cases of chronic rheumatoid arthritis according to the technique outlined by these authors. Two de-

partures from their technique were made. 1. The blood was collected and allowed to clot in the 500 c.c. Erlenmeyer flask in which the culture was to be made. Coagulation was allowed to take place with the flask in a tilted position so that the clot became adherent to the side of the flask and later could easily be broken up. After standing over night the expressed serum was drawn off with a pipet in one manipulation. The beef heart infusion broth used as the culture medium was then transferred to the flask in which the blood had been collected and had clotted. After the addition of the broth the clot was broken up into a number of pieces by strokes of a sterile pipet. 2. Subcultures were made at ten day intervals instead of five and during the month's incubation the flask was opened only three times. The same medium was used in making the joint cultures and they were subcultured also at ten day intervals. The results of our cultures are shown in the accompanying table:

Results of Blood Cultures

Rheumatoid arthritis,	70 cultures in 67 cases
Combined arthritis,	8 cultures in 8 cases
Atypical rheumatoid arthritis,	15 cultures in 15 cases.
Still's disease,	1 culture in 1 case.
Total,	94 cultures in 91 cases.

Organisms Obtained

1 Streptococcus viridans—	from a case of rheumatoid arthritis.
4 diphtheroids	—3 from rheumatoid arthritis.
	1 from atypical rheumatoid arthritis.
4 staphylococci	—considered contaminations.
3 gram positive bacilli	—considered contaminations.

Result of Joint Cultures

Rheumatoid arthritis,	14 cultures in 14 cases.
Results,	12 cultures negative.
	2 cultures contaminated with mould.

In only one instance was a streptococcus obtained, and this proved to be a *Streptococcus viridans*. However, we were unable to obtain this or any other organism when the culture was repeated. The diphtheroids occupy the usual uncertain position with regard to their significance. The staphylococci and gram positive bacilli were considered contaminations.

AGGLUTINATION REACTIONS

We then tested the sera of fifty-one cases of rheumatoid arthritis for the presence of agglutinins for hemolytic streptococci. These tests were placed in the water bath at 56° C. for two hours, then transferred to the ice bath where they remained during the night and were read the following morning. The sera were routinely tested for the presence of agglutinins to AB₁₃, a "typical" strain obtained from Cecil, Nicholls and Stainsby and for the scarlet fever strain, NY₅. Our results are shown in the accompanying table. In our series forty-six, or 90 per cent were found to possess agglutinins in their sera in the dilution indicated in the table. However, the extent of the dilution in which agglutination was obtained was somewhat lower

than that reported by other observers. Six per cent did not show any reaction.

SKIN REACTIONS

In order to determine to what strain of streptococcus our cases of rheumatoid arthritis showed the maximal skin reaction, we subjected fifty-five cases to intradermal tests. The tests were not done for the purpose of comparing either the frequency or the intensity of skin reactions in arthritics with those in non-arthritics, therefore we have no series of controls. Our object was to determine to what strain and type of streptococcus the patients of our series showed the maximal skin reaction, and to use this information as a guide to vaccine treatment. We confined the tests to streptococcal antigens not because these organisms have frequently been recovered from the blood and joints by others although completely missed by us, but because of the presence of serum agglutinins for hemolytic streptococci as uniformly demonstrated. The antigens used in the tests were prepared from strains of streptococci, both hemolytic and green,

Results of Agglutination Tests With Strains of Hemolytic Streptococci.

	Total Cases	Total Positive Agglutinations	AB ₁₃		NY ₅	
			A.	HK.	A.	HK.
Chronic rheumatoid arthritis	51	46	41	39	42	39

Highest Dilution of Sera in which Agglutination Occurred.

	Dilutions						
	1-20	1-40	1-80	1-160	1-320	1-640	1-1280
AB _{13A}	1	2	10	11	8	5	4
AB _{13HK}	1	2	16	8	7	3	2
NY _{5A}	1	2	11	10	8	7	3
NY _{5HK}	2	7	10	6	5	7	2

A = living and H. K., heat killed.

obtained from foci of infection in arthritics; a green strain isolated from a knee joint, later referred to as "Tschetter;" AB₁₃, the so-called "typical" strain obtained from Cecil, Nicholls and Stainsby; and stock laboratory strains. No tests were made with autogenous strains. The organisms were grown in meat infusion broth for twenty-four hours. A portion of the culture was then centrifuged and the precipitated organisms suspended in salt solution. The whole organism was used in preparing the antigen and appropriate dilutions were made, so that 0.1 c.c. of the salt solution suspension contained approximately one million organisms. The suspensions were placed in the water bath at 56° C. for one hour, at the end of which time cultures were made and allowed to incubate for forty-eight hours. If the cultures remained sterile the antigens were then ready for use. No preservative was added. The patients were tested with from fifteen to twenty antigens prepared in this way. One-tenth of 1.0 c.c. of the antigen was injected intradermally on the volar surface of the forearm and the results were read from eighteen to twenty-four hours later. An area of erythema 1 cm. in diameter or larger was considered a positive reaction. In most instances the reaction was larger, varying from 1 to 5 cm. in diameter,

in the center of which was an area of induration varying from 0.5 cm. to 2 cm. in diameter in direct proportion to the size of the area of erythema. In all instances the reaction was tuberculin-like in appearance, and in one instance was sufficiently violent to progress to the stage of necrosis in the central area. A total of fifty-five cases of chronic rheumatoid arthritis were tested, the results of the tests being shown in the accompanying table.

Skin Reactions to Intradermal Injections of Streptococci.

Total number of cases	55
Number reacting to hemolytic streptococci alone	24

Strain AB ₁₈ maximal in 6—Cecil strain	
“ “Maith” maximal in 5—Septicemia	
“ NY ₅ maximal in 7—Scarlet fever strain	
“ “Lee” maximal in 6—Septicemia with arthritis	
Number reacting to viridans streptococci alone	3
Strain “Lindsay” maximal in 2	
“ “Waller” maximal in 1	
Number reacting to both types of streptococci	28
Reaction of hemolytic streptococci maximal in	25
Strain AB ₁₃ maximal in 2	
“ NY ₅ maximal in 7	
“ “Maith” maximal in 10	
“ “Lee” maximal in 6	
Reactions to viridans streptococci maximal in	3
Strain “Giordani” maximal in 1—Bac. Endocarditis	
“ “Tschetter” maximal in 2—Joint	
Total number with maximal reaction to hemolytic streptococci	49 cases—90%
Strain AB ₁₃	8
“ NY ₅	14
“ “Maith”	15
“ “Lee”	12
Total number with maximal reaction to viridans streptococci	6 cases—10%
Strain “Tschetter”	2
“ “Giordani”	1
“ “Lindsay”	2
“ “Waller”	1

It will be seen that in this series all the patients gave a positive skin reaction to at least one strain of streptococcus. The number of strains to which each subject reacted varied; in but three instances did a reaction occur to only a single strain; the average number of positive reactions was to four strains and the maximum number to twelve strains. In twenty-four instances, or 43 per cent, there was a positive reaction to one or more hemolytic strains only. No single strain predominated in causing the maximal reaction, these marked reactions being divided equally among four of the strains. In only three instances did a positive reaction occur to a viridans strain alone, and in two of these only single positive reactions were obtained. In twenty-eight cases positive reactions were obtained

with antigens of both hemolytic and green strains. In this group twenty-five showed the maximal reaction to a hemolytic strain, whereas in only three was the greatest reaction obtained with a green strain. The distribution among the hemolytic strains was not uniform, ten of the twenty-five showed the maximal reaction to "Maith" strain, obtained from a case of streptococcus septicemia; NY., the scarlet strain, and "Lee," a strain obtained from a case of streptococcus septicemia with arthritis, showed the maximal reaction in about an equal number, seven with the former and six with the latter; Strain AB₁₃ showed the maximal reaction in two instances. Therefore, in a series of fifty-five cases all reacting intradermally to one or more strains of the streptococci with which they were tested, forty-nine cases, or 90 per cent showed the maximal reaction to a hemolytic strain, whereas only six cases, or 10 per cent showed the greatest reaction to a green strain.

We shall make no attempt to interpret these results in terms of causation but wish merely to record our results. These results were useful for our purpose since they indicated clearly to which particular strain of streptococcus among the many used each patient was especially sensitive.

VACCINE TREATMENT

The problem we had set ourselves was to determine what changes would occur in the diseased joints concomitantly with a gradual reduction of skin sensitiveness following the repeated injection of the antigen to which the patient was especially sensitive. An analogous situation exists in certain instances of choroiditis. The lesion is essentially inflammatory but non-specific. It is generally thought that these choroidal lesions are in some way related to tuberculous infection, but speaking strictly one cannot say that they are tuberculous, since they possess none of the characteristic histological features of tuberculous disease of the choroid. The assumption that they are related to tuberculosis rests chiefly upon the fact that these inflammatory reactions in the choroid occur nearly always in the presence of marked tuberculin hypersensitiveness as demonstrated by the intradermal test, although in most instances there is no demonstrable tuberculous disease elsewhere in the body. All that one can say definitely is that a choroiditis exists in the presence of a high grade of tuberculin hypersensitiveness, and that the lesions almost always do well when the patients are desensitized to tuberculin. Swift and his coworkers have shown that subcutaneous injections of killed non-hemolytic streptococci tend to sensitize rabbits, whereas injections given intravenously tend to make them immune. This observation decided us to use the intravenous route in giving the treatments. We were solicitous to avoid general reactions and at the same time to minimize the possibility of the effects of foreign protein shock reactions such as follow, for instance, the intravenous injection of typhoid vaccine.

The vaccine was prepared for each case from the strain to which the maximal skin reaction was obtained. It was a heat killed salt solution suspension of organisms, previously grown in beef infusion broth for twenty-four hours, so diluted for the initial dose that 0.5 c.c. contained approximately five million heat killed organisms. No preservative was

added. An intravenous injection of 0.5 c.c. was given as the initial dose and in most instances little or no constitutional reaction followed the injection. No set rule was followed in administering subsequent doses of the vaccine. The increase in dosage was gauged entirely by the patient's response. When any constitutional reaction occurred, manifested by fever, the dose was very slowly increased, keeping below the amount sufficient to produce fever. Otherwise the injections were made at four day intervals and each dose was increased by 0.5 c.c. If on account of a severe skin reaction it was feared that a constitutional reaction might occur, the strength of the initial dose of vaccine was decreased and the increase in dosage carefully gauged by the patient's response. In this way constitutional reactions were kept at a minimum, indeed almost entirely eliminated. During the first period of treatment the patients were kept in the hospital, in most instances in bed, a necessary precaution in many patients on account of the severe involvement of the knee joints. No other treatment was employed except the use of salicylates and sedatives as was necessary for the alleviation of pain. The injection of vaccine was continued at four day intervals during the stay in the hospital, which was from four to eight weeks' duration. Following discharge the interval was lengthened to seven days and the patients returned to the out-patient department for treatment, except in those instances in which the involvement of the joints of the lower extremities made this impossible.

Twenty-eight cases have so far been treated for periods ranging from two months to over one year. Of this number twenty-five patients had definite chronic rheumatoid arthritis, three suffered from combined arthritis in which the rheumatoid features predominated. In all cases symptoms and signs of the disease had been present for at least six months, the average duration being approximately two years. All foci of infection had been removed and sufficient time allowed to elapse to convince us that no benefit or further benefit would follow. Under treatment, twenty-one cases, or 75 per cent have shown evidence of definite improvement. The improvement manifested itself by reduction of pain, reduction of soft tissue swelling and increased mobility of the joint. In joints in which bone destruction and true ankylosis had occurred the mobility could not be increased but pain and soft tissue swelling were reduced. It has not been unusual to see fusiform swelling of the fingers decrease in size and in some instances disappear altogether. Eight patients were bed-ridden when treatment was begun; five of these are now out of bed and able to move about; two of the remaining three have been under treatment barely two months; the third has been treated for five months. The two under treatment only two months have shown definite improvement, whereas the one treated for five months has not been appreciably benefited. In all three cases there was extensive involvement of the knees. Although constitutional reactions have been absent or minimal, the patients have rather uniformly complained of focal reactions, indicated by increased pain in the involved joints for twenty-four hours after the injections. Following this reaction the joints have been less painful. Amelioration of symptoms has appeared gradually, becoming definite usually after from three to five

weeks, and from then on progressing slowly. The course of improvement has not been uniform in all cases; at times joints flare up during treatment but subside in a shorter time than is usual in the spontaneous remissions of chronic arthritis. Although improvement has not been obtained in all cases, in no instance has there been any untoward effect nor has an aggravation of the condition resulted from the treatment.

Seven cases have failed to show any definitely favorable response. In three of these we were disappointed because in the light of the response made by others it seemed reasonable to anticipate improvement. Two of these, however, have been under treatment only a short time. Two of the remaining five cases had long standing joint involvement with pain the chief symptom, whereas the inflammatory process was relatively burned out. In the remaining two cases a combined arthritis was present.

Twenty-six of the cases showing the maximal skin reaction to a hemolytic strain, have been treated with hemolytic streptococcus vaccine. In nine instances the "Maith" strain, obtained from a case of hemolytic streptococcus septicemia, was used. In nine cases NY₅, a scarlet fever strain, was used; in four, AB₁₃, a "typical" strain, furnished us by Cecil, Nicholls and Stainsby; in four the "Lee" strain, obtained from a case of hemolytic streptococcus septicemia with acute infectious arthritis. The viridans strains used were "Tschetter," isolated from a knee joint, and "Waller," a stock laboratory strain from an unknown source.

During the course of treatment the skin reaction to the strain employed has uniformly diminished in intensity and frequently disappeared entirely. The agglutinating power of the patients' serum has materially increased, and in those patients whose serum failed to agglutinate the organism used before treatment was begun, agglutinating power gradually developed. The increase in titer varied from 1-1280 to 1-10240 and was occasionally as high as 1-20480. In one of the cases in which a green strain was used agglutination was absent before treatment was given, but appeared shortly after and rose gradually until it was present in a dilution of 1-10240. In the second case no agglutination of the organism used in treatment has ever developed.

We determined the sedimentation rate of the erythrocytes in only a small number of our cases. In these few the rate decreased as improvement took place but in none did it reach normal.

COMMENT

Our efforts to recover streptococci from the blood and joints of cases of chronic rheumatoid arthritis have completely failed. In one instance a *Streptococcus viridans* was obtained but it was present for only a short time, and we feel this must be regarded as a transient bacteremia. In reporting these results we realize that the limited number of cases does not warrant any sweeping conclusions, but wish merely to record our failure to corroborate the work of those investigators who find streptococci in the blood and joints of a large proportion of cases of rheumatoid arthritis.

On the other hand the presence of agglutinins for hemolytic streptococci in the sera of patients suffering from chronic rheumatoid arthritis

seems well established. A positive reaction does not indicate of necessity a causal relationship between hemolytic streptococci and rheumatoid arthritis but it does suggest that streptococci play a rôle in the disease. Agglutination may be due to the presence of natural, not acquired or specific agglutinins,¹¹ but the frequency with which it occurs in rheumatoid arthritis is the most incriminating evidence thus far produced against the streptococcus in this disease and merits some consideration.

When skin sensitivity exists it does not necessarily indicate that there is also joint sensitivity or general sensitivity. The objections raised¹⁷ to the interpretation of skin reactions to autogenous vaccines; namely, that they may indicate varying irritability of the patients' skin, natural toxicity of the bacterial species or perhaps sensitization to certain bacterial groups, must be considered. However, the effect upon the reactions of subsequent treatment with vaccines indicates that they do represent a specific skin sensitivity to the strain used.

We are not prepared to offer an interpretation of the changes occurring after the intravenous injection of vaccine. We do not know that the diminution and disappearance of the skin reaction is a measure of desensitization, nor that the increase in the agglutinating power of the patients' serum is a measure of immunity. However, we do feel that the skin reaction is the most definite evidence of hypersensitiveness we could obtain and wish to cite the observations we have made and record the improvement which has taken place in the patients we have treated. We realize that any claim to specificity could justifiably be disputed, and that it is not beyond the realm of possibility that the improvement brought about in the result of treatment which is non-specific in character. We have succeeded in eliminating or at least minimizing the feature of non-specific therapy to which is commonly attributed the benefit derived from vaccine treatment. The evidence of improvement has appeared fairly early but the long continued use of vaccine may be of further value. Our series of cases is small and we present the results so far obtained for what they may be worth.

SUMMARY

1. The results of ninety-four blood cultures in ninety-one cases of rheumatoid arthritis are reported.
2. The results of fourteen joint cultures in rheumatoid arthritis are reported.
3. The sera of forty-six, or 90 per cent, of fifty-one cases of rheumatoid arthritis were found to possess agglutinins for hemolytic streptococci.
4. All of fifty-five cases of rheumatoid arthritis gave positive skin reactions to one or more strains of streptococci.
5. Twenty-one of twenty-eight cases of rheumatoid arthritis have shown improvement when given intravenous injections of streptococcal vaccine prepared from the strain to which they were most skin sensitive.

We wish to express our appreciation of the advice and assistance of Dr. William S. Tillett, in whose laboratory this work was done.

DISCUSSION OF PAPERS BY DR. STEINDLER AND DR. WAINWRIGHT

DR. J. ALBERT KEY, St. Louis: Since we are told no individual reaches adult life with normal tonsils and with normal teeth, it is unusual to hear that Dr. Steindler found foci in only about 17% of his cases of atrophic and hypertrophic arthritis. It is noteworthy that he found foci of infection as frequently in cases of hypertrophic, as in atrophic arthritis. Few believe that hypertrophic arthritis is a bacterial disease. Only a small percentage of his cases were cured by removal of infected foci. Considering the natural course of the disease we know that this many or more get better in spite of anything we do, and under a large variety of forms of treatment 50-60% of cases are improved.

With his vaccine Dr. Wainwright improves 75%. Most of us use vaccines in arthritis and I use them myself with the full knowledge that there is no disease of which I can find record (and we know the causes of a good many of them) which has been proven cured by vaccines. The patient insists that the physician do something and I think it is all right to give him vaccines provided you do not forget to treat him and his disease with additional accepted and indicated measures. The vaccine will keep the patient interested while we proceed with treatment for the general condition.

With regard to cultures of blood and joints I can't confirm anybody's results, not even my own. Some years ago I isolated staphylococci and diphtheroids. Sterilizing the skin better, I later failed to get the latter. We should condemn the habit of discarding all staphylococci as contaminants and considering the streptococci found as the cause of whatever disease we are studying. There is no more reason why arthritis should be due to streptococci than to staphylococci or diphtheroids. However, my own experiments convince me that the arthritis produced with streptococci and diphtheroids is more closely akin to human arthritis than that produced in animals with staphylococci.

DR. M. H. DAWSON, New York: I should like to congratulate Dr. Steindler on the massive amount of statistical data which* he has collected. Anyone who has the opportunity to study 4,339 cases of chronic multiple arthritis, of which over 3,000 cases were of the rheumatoid variety, has had a unique amount of material at his command. The large number of cases studied demonstrates most convincingly the widespread nature of the disease.

In the early part of his paper, Dr. Steindler stated that, in considering the significance of foci of infection in arthritis it was required, above all things, to compare the incidence of foci of infection in arthritis with the general incidence in non-rheumatic diseases. I therefore anticipated that we should hear some interesting comparative data on this phase of the subject. However, in the remainder of his paper, Dr. Steindler failed to refer to this matter. I should, therefore, like to ask him what his statistics reveal on this important point.

The subject of focal infection in chronic arthritis is a very practical one for any one who is concerned with the treatment of these patients. However, there is one most important point which I feel cannot be too strongly emphasized and that is, the distinction between rheumatoid arthritis and osteo-arthritis. We believe that rheumatoid arthritis and osteo-arthritis are two separate and distinct disease entities. We believe that osteo-arthritis is simply an age-period degenerative change not associated in any way with infection. Rheumatoid arthritis, on the other hand, is a disease intimately associated with infection. The remarks which I should like to make are therefore concerned with the significance of foci of infection in rheumatoid arthritis.

In agreement with Dr. Steindler's findings, we believe that foci of infection, particularly in the tonsils and sinuses, are of very considerable importance in rheumatoid arthritis. The removal of such foci of infection, particularly early in the course of the disease, is often attended with brilliant results. In further agreement with Dr. Steindler's observations, it is our feeling that infection by way of the gastro-intestinal tract plays a small rôle in the production of the disease. We particularly agree with his remark that the significance of abnormalities of the gastro-intestinal tract remains at least uncertain.

With regard to the matter of dental infection I feel that a moderately conservative attitude should be adopted. Dental infection undoubtedly frequently plays a rôle in the production of much "focal" arthritis and in the various forms of "non-articular rheumatism." However, I am not at all convinced of its importance in the production of the clinical disease rheumatoid arthritis.

In discussing the results of removal of foci of infection, Dr. Steindler has presented us with some very interesting facts. He quoted two series of statistics, one assembled by Miltner and Kulowski, and his own. In the series by Miltner and Kulowski, no improvement occurred in 91% of the cases of osteo-arthritis. In his own series, he states that eradication of foci of infection in the "hypertrophic type does not, on the

whole, materially affect the results." These findings are entirely in accord with our own experience and I feel that they cannot be too strongly emphasized. It is our belief that foci of infection should not be sought in osteo-arthritis except as part of a general health examination. If found, their removal is only indicated as a general health measure.

Finally, I should again like to express my admiration of the impressive amount of material which Dr. Steindler has collected.

The results of cultures on the blood and joints of patients with rheumatoid arthritis which Dr. Wainwright has presented agree entirely with the findings which we published several years ago. At that time we reported that we had never been able to demonstrate the presence of organisms in any significant number of cases.

Dr. Wainwright's agglutination studies are also in accord with our own observations. The fact seems to be well established that the serum from the majority of cases of rheumatoid arthritis possesses the capacity to agglutinate hemolytic streptococci. Furthermore, this agglutinating capacity is not related to the non-specific agglutinating property exhibited by the sera of many acute febrile diseases. In this connection we recently carried out a "blind-fold" agglutination test on a large number of sera sent to us by a well-known arthritis clinic. The results of this test demonstrated that it was possible to identify the sera from patients with rheumatoid arthritis in a high proportion of cases.

More recently we have extended our agglutination studies to include precipitin tests. Various protein and carbohydrate fractions of *Streptococcus hemolyticus* have been employed. The results of these studies show that there is a close approximation between the capacity of rheumatoid arthritis sera to agglutinate hemolytic streptococci and to precipitate various fractions of this organism. We do not believe that the immunological reactions establish the etiology of rheumatoid arthritis but, as Dr. Wainwright has said, they constitute the most incriminating evidence which has thus far been brought forward against *Streptococcus hemolyticus* in this disease and merit careful consideration.

In our experience skin reactions in rheumatoid arthritis are very variable and difficult to interpret. In a limited series of observations we were unable to demonstrate any correlation between the degree of skin reactivity to various strains of hemolytic streptococci and the clinical condition of the patient. Furthermore, it is our feeling that sufficient evidence has not been brought forward to indicate a relationship between skin reactivity and the reactivity of joint tissues. There is suggestive evidence, however, that rheumatoid arthritis patients do, as a group, show a higher degree of skin reactivity to *Streptococcus hemolyticus* than do patients suffering from other diseases.

Finally, a few words regarding the therapeutic results which Dr. Wainwright has reported following the use of intravenous vaccines. He has stated that 21 out of a series of 28 patients so treated received definite benefit. However, as he himself mentioned, there was no control series and the treated patients received the additional benefit of four to eight weeks' rest in bed. It has been our experience that an equally large proportion of cases show definite improvement on a regime of adequate rest alone. During the past five years we have used hemolytic streptococcus vaccines on a large series of rheumatoid arthritis patients. The methods of administration and the dosages employed have been quite comparable with those just reported. It has been our experience that the value of this form of therapy remains unproved.

DR. RUSSELL L. CECIL, New York: May I say a word about the present status of the bacteriology of atrophic arthritis? We can divide the results so far reported into three groups: 1. The work of those in which streptococci are found in the blood and joints of patients with rheumatoid arthritis but not in controls. 2. The group in which the studies of Dawson and Boots, and of Dr. Wainwright belong, who find practically all blood cultures and joint cultures sterile in both controls and patients with rheumatoid arthritis. 3. The group represented by Dr. Callew's recent study on rheumatic fever and May Wilson's report on blood cultures in children with rheumatic fever, in which a high percentage of streptococci are found both in patients with rheumatic fever and in controls. It all goes to show how confused the whole problem is.

No one wants to get to the truth of this matter more than we do. If the streptococci which we and others have recovered are only contaminations, we want to know it. The question is far from solved. I don't think I am misquoting Dr. William H. Park in saying that he believes the streptococci which have been isolated have been actually in the blood, but he is very conservative and cautious about their interpretation. We recently asked Dr. William Elser to help us on this problem. Dr. G. I. Steffen took blood cultures on some of our arthritis under the most carefully controlled conditions. In a dozen or more typical cases of rheumatoid arthritis he got about 50 per cent positive blood cultures, but only one streptococcus. The other organisms recovered were all

diphtheroid bacilli. These latter have some interest in view of claims that they can be transmuted into streptococci.

It seems to me that nature would be playing a mean trick on us if an organism that appears so frequently in blood cultures, that apparently produces immune reactions in the patient's serum, and that produces such a typical experimental arthritis in animals, would turn out to be nothing but a harmless contaminant.

DR. RUSSELL L. HADEN, Cleveland: Dr. Wainwright's paper emphasizes one significant trend that regardless of the isolation of this or that germ, or treatment by this or that method, our chief problem is to study the patient and see what happens to him. Dr. Wainwright talks of the patients' hypersensitivity. According to numerology a patient is supposed to be sensitive to certain things because he was born under certain circumstances. In considering the problem of chronic arthritis it would appear that certain "normal persons" are not and perhaps never will become sensitive or liable thereto while another individual will. In addition to isolating organisms and removing foci we must study the other underlying characteristics of the patient. The correction of his altered soil may be more important than removing a focus which is but the beginning of treatment.

DR. JOSEPH L. MILLER, Chicago: Physicians of this country have been slow to recognize the essential differences between atrophic and hypertrophic arthritis. It seems almost certain that they are two distinct diseases, hypertrophic arthritis being merely a degenerative disease. The rapidity with which certain patients get well after removal of an infected tooth makes me think there is at times a profound psychological effect therefrom. I saw one arthritis patient recently who four weeks before had a bad tooth removed. Before she got home from the dentist she was "all well." Recently she read of somebody dying of arthritis and now her pain is back. Regardless of such instances, however, I approve of the removal of foci and the use of vaccines in addition to other measures of recognized merit.

DR. STEINDLER: Many of our 4,000 cases, as I have mentioned, were unable to have a complete focal check for various reasons. At least 900 patients did have a complete search for foci, and of this group between 15 and 35 per cent had a satisfactory response following removal of foci. By response I don't mean cure; I mean that they obtained subjective relief that was maintained for a considerable length of time.

I also mentioned the normal incident of diseased tonsils and sinuses in non-arthritic cases, which answers Dr. Dawson and Dr. Key. The response in hypertrophic cases was one-half that in atrophic, or 8 per cent.

DR. WAINWRIGHT: May I say to Dr. Key that we feel that our vaccine has more than a psychic effect. Not uncommonly patients develop a degree or two of fever with the initial injection, but when this occurred the subsequent dose was lessened or at least not increased and generally no further febrile responses were noted. Occasionally a particularly sensitive patient would experience a febrile reaction after the first three or four injections. In such cases much smaller doses were used until the reactive phase disappeared.

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THE MANAGEMENT OF ATROPHIC ARTHRITIS IN RELATION TO THE DIFFERENT PHASES OF THE DISEASE

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Insufficient attention has been paid to the variations of management necessary during the different phases of atrophic arthritis. Many good therapeutic aids have not only been used unwisely but often have been discarded because of their use at the wrong time. Massage and a low starch starvation diet in the acute phase of the disease are typical examples. It should be remembered that atrophic arthritis may be initiated with all the acuteness of rheumatic fever,—indeed, at its onset, differentiation is often impossible or it may begin almost insidiously with very few symptoms. The course of atrophic arthritis may vary from a rapidly progressing febrile and exceedingly severe illness, in which the patient becomes helpless almost immediately, to an afebrile illness with but little discomfort over a period of years but which may just as certainly go on to a crippling deformity.

Because of these wide variations in onset and course, it seems advisable to consider the therapeutic measures in relation to the stage of the disease. It is the purpose of this paper to suggest a scheme of management adaptable to the various phases. This routine of management has grown out of our experience in treating a large number of these patients over a prolonged period of time.

Our concept of atrophic arthritis does not admit a known single specific etiologial agent, nor therefore a specific cure. There are a great many factors concerned in the etiology of this disease, a disease not only of the joints but also constitutional, manifesting itself in almost every system of the body.

We have previously reported carefully controlled experiments with various types of therapy. This consisted of placing approximately four hundred patients with atrophic arthritis on a program which included diet, bowel managment, prevention and correction of deformity, rest, exercise, general physiotherapy, and climatotherapy.

After a control period of several months one hundred had foci removed, one hundred were given blood transfusions, one hundred were treated with vaccine, and one hundred were given special heliotherapy. Progress was observed over periods ranging from months to years. The results of this study emphasized the non-specificity of any *single* therapeutic agent used. It is, then, our viewpoint that the therapy of atrophic arthritis should concern itself first of all with the patient's general health. It is of the utmost importance to study and to regulate his daily life to the minutest detail, recognizing that the best results can be secured only by a comprehensive scheme of management. When a patient presents him-

self for treatment, it becomes essential to devise an ideal program, and this must be done for each patient individually. Because of the wide variation in the severity of symptoms and the difficulty of determining at once the phase of the disease, we have adopted the plan of treating each new patient as an acute case, and then as rapidly as possible advancing him to the stage of activity for which he is ready. This will mean a few weeks of bed rest for patients who have been quite active, but it is much safer than permitting a patient activity for which he is not ready. We have found this system of management, including graded amounts of rest and corrective exercises, most valuable.

Some of the therapeutic procedures which vary during the different phases of the disease will be discussed briefly.

GENERAL MANAGEMENT

Constitutional management must include a general program that will aid in combating the disease by treating the patient both physically and mentally. Before the onset of arthritis it is exceedingly common to find that there has been a history of increasing business or domestic troubles, nervous strain or shock, over-work, irregular hours, constipation, loss of weight and many other factors that are not conducive to good health.

In view of such a history, the treatment at the onset, or in the first phase of the disease, should be directed toward establishing a correct routine of living. This may mean partial or total elimination of business or domestic responsibilities, avoidance of conditions producing nervous strain, and establishment of regular hours; all in addition to the correction of the many physical defects. Ordinarily, if it is possible, the patient will do better and save more time if at the onset he is away from his family and business and is started on a full program—making it his business to get well.

One of the first essentials in treating a patient with atrophic arthritis is a complete understanding between patient and physician, for it is only with the patient's understanding and coöperation through such a long and chronic illness that one can hope for any degree of success. Each patient should be told honestly what the problem of adequate treatment includes and that there is no easy way. Unfortunately arthritis is usually chronic, often lasting many years and ultimately, if not treated, may end in crippling deformity. Regardless of treatment there may be recurring periods of exacerbation and remission. With such a disease it is only natural that most patients become pessimistic and discouraged. When a focus of infection is not found, or if the patient does not get the improvement expected after removal of infection, he often becomes discouraged and thinks his disease is incurable. It must be remembered that many patients have gotten well when there was no infection found or in spite of remaining foci of infection.

The amount of rest and general activity depends entirely upon the severity or phase of the disease process. In the acute or progressive phase of the disease rest is most essential, for it allows healing and promotes relaxation of spastic muscles. In the severe form the patient is of course

at complete bed rest. In general, as the disease process subsides the patient is allowed more physical activity and is made to increase his corrective exercises. The amount of exercise and physical activity should be pushed to tolerance, which may be roughly determined by the presence of increasing fatigue or pain that persists during rest after exercise. The patient may be guided by the rule that pain during exercise is of little or no significance provided it does not continue after exercise. In the course of the disease, certain guides such as fever, local joint heat or redness, swelling, and sedimentation rate are of value for the determination of the degree of disease activity. By constantly watching the various guides indicating the severity of the disease, the amount of rest, exercise and general physical activity should be determined. Depending upon the fluctuation in the disease activity there will be constant changes necessary in the rest-exercise ratio. These changes should always be gradual.

To sleep at night is almost always difficult and the patient must be given every aid. Some are able to learn to sleep in good posture but the majority will have to change position frequently to get relaxation of spastic muscles. Proper sedatives should be used for nervousness. Splinting acute or deformed joints in correct posture and the administration of acetylsalicylic acid is usually all that is necessary to relieve pain and muscle spasm. Local heat to aching muscles is helpful.

The daily routine should include regular periods for corrective exercises two or three times a day, periods for resting and periods for recreation or work as the patient can tolerate them.

The amount of general activity allowed should be maximal provided that it does not increase the disease process nor tend to create deformity. This means that the patient should be encouraged to care for himself as much as possible, as in eating, bathing, dressing, etc. As he is able to do these things for himself without increasing pain or fatigue he will gain confidence and work harder for a cure. Straining excessively at any task, such as getting up from low chairs or climbing stairs, is harmful and should be prohibited. When the acute phase has subsided and the patient is allowed to be up, the bed, chairs, and toilet seat should be high enough to permit rising without strain. In all of the daily activity the best possible posture must always be kept in mind. Reading and writing in cramped positions for long periods are harmful. Occupational therapy as tolerated should be encouraged and well chosen, depending upon the extent and severity of the involvement.

In our experience, patients in the beginning do not adhere rigidly to a program unless they are under daily supervision of trained personnel.

DIET AND NUTRITION

Most patients with atrophic arthritis are undernourished. Correction of the malnutrition, present so frequently in the early or acute phase, is most important, and is one thing that can be done toward raising resistance to combat the disease. General improvement will often be in direct proportion to the patient's ability to regain normal weight.

When the patient is underweight, a high caloric, high vitamine diet with plenty of red meat, starches, fresh fruits and green vegetables should

be given. Extra vitamins are given by the addition of yeast, wheat germ, and cod liver oil. Liver and iron in large doses are given to correct anemia. A weight producing diet alone is not always sufficient, and other measures must be used such as rest in bed, hot wet packs to the abdomen after meals, intermediate nourishment, belladonna, dilute hydrochloric acid, and sometimes insulin. Where one or several of these measures fail, all put together usually succeed.

After gain to normal body weight, or in maintaining body weight, the low starch high vitamin diet is used. Free sugar, bread, potatoes, etc., are eliminated. Adequate protein, large quantities of fresh fruits, green vegetables, and extra vitamins should be continued.

The low starch and low fat diet for reducing the occasional patient with obesity is readily adaptable to the management of arthritis.

BOWEL MANAGEMENT

Cathartics are best avoided, for although they may give temporary relief they usually lead to an increasing constipation. It is important to have adequate and regular elimination daily, and for this mineral oil, agar agar, oil retention enemas, and glycerine suppositories usually will be sufficient. Regular habits, chest and abdominal exercises, knee-chest position, rectal dilators, etc., all have their advantages. When the stool is alkaline, it is often advisable to change the reaction to acid. This may be accomplished by various lactic acid preparations. High enemas or colonic irrigations are of questionable value.

PREVENTION AND CORRECTION OF DEFORMITY

In every patient with atrophic arthritis the possibility of residual deformity in any or all involved joints should be anticipated. The prevention of such deformities can be accomplished only at the price of eternal vigilance, and their correction requires infinite patience. If the patient is seen early enough in the disease, the problem will be one of prevention only. The chief deformities occur in flexion, particularly in the knees, hips, elbows, wrists, hands, and spine. Unfortunately, the patient usually selects the worst possible position. He lies on a bed that sags, placing pillows under his knees and head. The hands, wrists and elbows lie flexed across the body. Thus, deformity begins. More than 80 per cent of all patients with chronic atrophic arthritis entering our clinic have a flexion deformity of one or more joints which could have been prevented.

The first requirement is a hard bed that does not sag. The patient must spend several periods during the day on this bed without pillows and with all joints full extended. If pain or muscle spasm interferes, plaster shells for the knees and splints for painful joints such as cock-up splints for the wrists should be used. Chest, abdominal and postural exercises are invaluable at this stage of the disease. Assistive exercises, which move every joint through its full range of painless motion at least once daily, should be begun early. Group muscle exercises, particularly of the extensors, such as the patellar pull, should be begun even before any joint motion is possible. As active inflammation subsides, exercises should be active and not passive, becoming increasingly strenuous. It is entirely possible to reach the muscular development of an athlete by bed exercises alone. It is es-

sential that posture be correct, knees straight, and sufficient muscle strength be developed before the patient is allowed to begin walking. Properly fitted shoes with good arch supports, horse shoe pads and ace bandages to the knees, and a pair of crutches properly used, when walking is first attempted, will allow a patient to succeed. Otherwise he may be forced to return to his bed in disappointment. It is especially important in the early stages of the disease that no weight be borne on a bent or painful knee. This only results in further damage to inflamed joint structures and is often the cause of irreparable damage.

If there are flexion contractions of the knees or other joints, a series of plaster shells will usually provide sufficient relaxation to secure a correction of the deformity. Failure to secure complete correction may be due to a capsular adhesion or a villus arthritis impinging on the articular surface of the joint. A capsular adhesion may be corrected by capsulotomy or, in many instances, by careful manipulation under anesthesia. This should not be attempted until the joint has been without evidence of active inflammation for at least six months. The problem of villus arthritis of the knees is more difficult of solution. We have used with some success horse shoe pads and ace bandages together with knee exercises for the correction of subluxation. A prolonged period of rest from weight bearing occasionally will permit full painless extension and painless weight bearing. A number of men have advocated synovectomy in such cases. We feel that inflammation in the joint should be quiescent for at least a year before synovectomy is considered and then it should be performed only with the advice of a competent orthopedic surgeon experienced in arthritis.

It may require months or years to correct deformities once they are established and even if one is successful such a joint is often not as useful as one in which no deformity has occurred.

GENERAL PHYSIOTHERAPY

The local application of heat to the joints is a much abused therapeutic procedure. Heat to the joints should not be utilized early in the disease as it is often responsible for prolonging an active process which might otherwise subside. It certainly should not be used in the acute stage when there is heat or redness in the joint, and it should be begun very cautiously in the early chronic stage of the disease. Heat to muscles often relieves pain and may be used cautiously in early stages. We feel that diathermy is usually harmful when used in the presence of the marked demineralization which is usually present in atrophic arthritis. We reserve diathermy for use in hypertrophic arthritis. Contrast baths to the hands or feet are especially useful in the presence of cold, clammy, and wet extremities. The dry, aching joint or extremity responds well to paraffin packs. Cold Epsom salts packs will often reduce pain in the acute stages, while the hot Epsom salts packs or hot salt and sand packs are useful in the chronic stages. In addition, the large salt and sand pack, because of its weight and heat, may assist in correcting a slight residual flexion contraction of the knee.

REMOVAL OF FOCI OF INFECTION

Removal of foci of infection should be considered with regard to the phase of the disease. If this is to be of any benefit it ought to be accomplished early in the disease, but it is exactly here that it is most hazardous. We have observed a large number of patients who had a definite spread of their disease with acute exacerbations following removal of foci. Patients in the early stages of atrophic arthritis usually have a history of fatigue, nervous exhaustion, constipation, and malnutrition. It seems only reasonable that a fair attempt should be made to correct these factors, which have made the development of the arthritis possible, before risking the surgical insult associated with radical removal of foci. Such patients should be treated for a reasonable time in an attempt to lessen the severity of the disease and improve the patient constitutionally, and then under the best possible conditions foci may be removed. Certainly in the severe cases where the patient is undernourished, fatigued and nervously exhausted there is a very great hazard in immediate removal. When foci such as teeth or tonsils are removed, the infection itself is not removed at once but invades the lymph nodes and tissues about the focus. Absorption is actually increased for a time. Frequently we precede the removal of foci by a transfusion and take particular care not to remove a focus during or near an acute phase of the disease. We have seen few unfavorable reactions following removal of foci since following this plan. If foci of infection are removed in the very chronic afebrile cases with advanced joint changes, it should be done because of general health considerations and not with the hope of curing the disease.

VACCINES

We have given vaccines, using autogenous and stock antigens by the intravenous and subcutaneous routes. Improvement not easily accounted for otherwise, occurred only occasionally. We have had some favorable results in the sub-acute phase of the disease by giving intravenously, minute doses of antigen to which the patient was strongly skin sensitive. Non-specific protein shock therapy or marked reactions from vaccines of any kind are often responsible for exacerbations of the disease. Particularly are such measures to be condemned in the sub-acute phase.

TRANSFUSIONS

Patients with fever in the acute or sub-acute phases of atrophic arthritis, with or without anemia, respond well and occasionally dramatically to a series of small blood transfusions. Transfusion has been of little help in the very chronic afebrile patients with far advanced joint changes.

CLIMATE

Of the many climatic components, sun radiation is the one over which we have most control. Heliotherapy in various forms has an important place in treatment but it must be given judiciously under proper supervision. In the active phase of the disease or in the presence of fever it is usually too stimulating, and causes an increase in fever, pulse rate, and sometimes produces dizziness, nausea and vomiting. When acute, the disease is best treated by air baths or exposure to sky shine.

When the disease is less active, general sun exposure is started for one minute, front and back, or by the Rollier technique. The exposure is then gradually increased, watching the temperature and pulse periodically to note and prevent reactions. Tolerance varies not only with the phase of the disease but with the individual so that exposures may run from several minutes to an hour or two.

The exact nature of the physiological response to heliotherapy is not as yet clearly understood. Symptomatically, the patient notices a general tonic effect with marked relief from aching and muscle spasm. Circulation is improved, and the extremities become warm and lose the characteristic clammy feeling. The hemoglobin and red blood cells are increased. The Thezac lens is used to concentrate the sun rays and give local heat to affected joints and muscle groups. This is used in the less acute phase and of course with care because of its marked stimulating quality.

It must be understood, however, that, without a proper routine of living, arthritis, even on the Tucson desert, can continue as a sad and crippling disease. Unfortunately, many people come to the southwest believing that climate performs miracles and with the idea that a month or so in the Arizona sun will cure them. These individuals if not put under supervision often get an unfavorable and sometimes serious sun reaction from over-exposure.

We have previously reported some brief observations indicating a definite climatic advantage in the treatment of atrophic arthritis on the Tucson desert. The following evidence was presented:

(a). There is a low incidence of atrophic arthritis in local Indians, as compared with similar tribes elsewhere.

(b). There is a low incidence of atrophic arthritis in native residents in the vicinity of the Tucson desert.

(c). In a group of 100 patients with atrophic arthritis, gratifying results were obtained in a large proportion without resort to any specific therapy other than the general measures described and climatic treatment. It is our belief that, inasmuch as most of these patients had tried nearly every other known remedy, the satisfactory results can in a large measure be ascribed to carefully supervised climatic therapy.

We shall present a typical case history illustrating a few of the necessary changes in management during the course of the disease.

Male. Aged 58. Chief complaint:

1. Pain, swelling and deformity of both hands, wrists, knees and ankles. Pain and limitation of the left hip, shoulders and neck. Patient almost entirely helpless, unable to feed himself or to get off bed. Duration one year.
2. Weight loss, thirty pounds.

Physical Examination: (Positive findings)

1. Joints mentioned show marked limitation of motion, several show effusions and one is red and hot. Flexion contraction of both knees and wrists.
2. Malnutrition.
3. Fever, 100-100.5 F. daily. (Patient denied fever).

4. Anemia.
5. Irritable bowel with constipation.
6. Foci: Dental sepsis and chronic cholecystitis.

Laboratory: (On entry)

1. R. B. C. 4,000,000.
2. Hemoglobin 75% (Sahli)
3. W. B. C. 14,000. Schilling 0/0/0/83.5 Monocytes 2 Lymph 14.
4. Sedimentation R. B. C. 77 mm. in 1 hour. Temp. 21° (Westergren)
5. Stool: alkaline.
6. Gastric analysis: free HCl absent.

X-Ray:

1. Marked demineralization of bones of hands, knees, pelvis, feet and cervical spine.
2. Cartilage destruction of knees and between tarsal bones.
3. Diverticulum of sigmoid with spasm.
4. Thickened, poorly functioning gallbladder.

TREATMENT IN THE ACUTE PHASE

1. Bed rest.
2. Plaster shells to correct flexion contraction of knees and prevent muscle spasm.
3. Cock-up splints for wrists.
4. Firm, non-sagging bed.
5. Semi-bland, high caloric, high vitamin diet.
6. Dilute hydrochloric acid, one teaspoonful with meals.
7. Lactic acid emulsified in agar and mineral oil, two ounces every night.
8. Hot wet packs to the abdomen after meals.
9. Tincture of belladonna to tolerance, three times daily.
10. Corrective exercises: every joint assisted through its full range of *painless* motion daily. Postural position, abdominal and breathing exercises. Group muscle exercises without joint motion.
11. Salicylates for relief of pain.
12. No heat. No massage.
13. Four transfusions (after eight weeks control period, fever daily) of 250 c.c. each.
14. General climatic advantage and graduated air baths.

At the end of three and one half months patient had gained seventeen pounds, had a normal temperature, and had very little spontaneous pain. Hemoglobin had risen from 75 to 90% and the sedimentation rate had dropped from 77 to 35 mm. Routine was changed and the following orders were given:

1. Change diet to one limiting concentrated starches. Add large amounts of green vegetable and fruits.
2. Light massage, gradually increasing. Avoid joints.
3. Group muscle exercises. Increase active corrective exercises, assisting only when necessary; full range daily. Stress patellar pull and foot exercises. Continue posture, breathing and abdominal exercises.

4. Heat to joints and muscles cautiously (no diathermy).
5. Heliotherapy, general and local, cautiously and under close supervision.
6. Water (pool) exercises. Water walking.
7. Contrast baths to hands and feet.
8. Dental extractions.

After eight months the patient had gained twenty-five pounds. Hemoglobin was up to 100%, and sedimentation rate had dropped to 20. Knees were straight. Patient was able to move nearly all of his joints actively through a fair range. The following routine was added:

1. Allow to stand on feet with
 - (a). Corrective shoes with supports
 - (b). Horse shoe pads and ace bandages to knees
 - (c). Crutches
 - (d). Calipers for a short time (not often necessary)
2. Carefully instruct in correct posture and use of crutches as walking is begun.
3. Increase all corrective exercises and allow gradual increase in walking.

After fourteen months, weight gain maintained. Sedimentation rate down to 6. Patient was walking freely with a cane. He returned to his home in a mid-western city.

Patient was re-examined after a period of thirteen months of full business activity. No sequelae except deformity of one finger. No return of symptoms. Treatment now consists of regular hours, Saturday and Sunday rest, full corrective diet, bowel regulation, and corrective exercises. The remaining foci (gallbladder and bowel) were treated conservatively. Following general recovery the gall bladder findings returned to normal by x-ray and clinical standards.

This is an average case history showing the management of unquestionable atrophic arthritis through its various phases. This patient made a recovery in approximately fourteen months. Some patients respond more rapidly to treatment and others much more slowly. Occasionally the disease remains progressive for years in spite of treatment. A very chronic case of several years' duration will usually respond to this same routine but more slowly. Patience and effort will often accomplish a happy result in spite of the most hopeless outlook.

SUMMARY

A brief summary of the management in the various phases of atrophic arthritis has been presented. Only the following more common and important factors have been discussed: (a) general management; (b) diet and nutrition; (c) bowel management; (d) prevention and correction of deformity; (e) general physiotherapy; (f) removal of foci of infection; (g) vaccines; (h) transfusion and (i) climate.

Emphasis is placed on the necessity of a broad, comprehensive outline of treatment individualized for each patient.

In addition to the general treatments discussed, we recognize that we are favored with a climatic advantage in the Tucson area.

A typical case history is given showing the variations of management during the different phases of the disease.

DISCUSSION OF PAPERS BY DRS. HOLBROOK AND HILL

DR. ROBERT B. OSGOOD: Dr. Holbrook and Dr. Hill have ably set forth their views as to the generalized nature of the disease and as to the rational approaches to its stronghold which must be overcome if the disease is to be controlled. I do not quite agree with them when they say that "regardless of treatment there are recurring periods of exacerbation and remission." I quite agree that periods of exacerbation and remission often occur in spite of treatment but not all cases go through these periods nor is such periodicity regular. When our therapy becomes more intelligent and mental and physical extraneous conditions can be controlled, we shall not need to consider such exacerbations as inevitable. In connection with the short paragraph on the management of the bowels it seems to me that they might well have mentioned abdominal massage after the Drown method and Hugh Owen Thomas' cure for constipation. This consists in making the foot of the bed six inches higher than the head, whereby ptosed and kinked intestines crowded into the pelvis may be given more room to function during the night of recumbent relaxation. These mechanical measures I have found to be strong adjuvants in improving alimentation. I find myself in accord with the authors' views as to the removal of foci of infection and the employment of vaccines. When the attitude of clinicians in general toward chronic arthritis becomes as sane as that of Dr. Holbrook and Dr. Hill, it seems reasonable to hope for fewer tragedies and more successes in the management of the different phases of chronic atrophic arthritis.

DR. ERNEST E. IRONS, Chicago: To me these papers have been wonderfully instructive and have included many stimulating suggestions and indications for treatment. We must rightly emphasize that arthritis is a general disease and requires for its treatment an attack from many angles.

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1. Holbrook, W. P.: Evaluation of therapy in chronic atrophic arthritis. *Ann. Int. Med.* 7: 457 (Oct.) 1933.

CHRONIC ARTHRITIS IN CHILDREN*

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Chronic arthritis in children, though not common, is a serious problem in that it frequently condemns the individual to a life of total invalidism and economic dependence. Particularly is this true of generalized proliferative or atrophic arthritis, which when associated with enlargement of the spleen and lymph glands, is commonly called Still's disease. The disease in children has much in common with the severer type of atrophic arthritis seen in adults, in the distribution of the joints involved, the appearance of the joints themselves, and the pathology presented. Frequently in children, the disease is more fulminant in character with pronounced febrile phases; it may be slow and insidious in onset. Instead of a generalized involvement of all joints, a single joint may be involved.

The disease may arise any time after the first year of life; our youngest case was thirteen months at the onset. It is more common after the second year.

It is the intention of the writers to present for your consideration the methods of approach and treatment of those cases which come to the Boston Children's Hospital. No claim is made that a specific cause or cure has been discovered. It is our experience, however, that if these patients can be safely guided through the active stages of the disease, the process becomes arrested and quiescent and one may expect improvement. It is the proper path through this active phase with which we are particularly concerned here.

METHODS OF PROCEDURE ON ENTRANCE TO THE HOSPITAL

The patients with multiple joint lesions are usually extensively crippled, and frequently thin and emaciated at the time of admission to the hospital.

A complete history is taken, including familial and social background. In the past history, particular emphasis is placed on dietary and gastrointestinal factors throughout the child's life, and infections, particularly those which are contiguous with the onset of the disease. Inquiry is made concerning allergic manifestations, both familial and individual.

The physical and laboratory examinations are made as searching as possible. All possibilities of focal infection are considered and investigated, such as, the throat, teeth, sinuses, and chest. Routine cultures are made of the throat and stools, as well as such other cultures as may be indicated. Vaccines are prepared of suspected organisms and sensitivity to these organisms is tested. Many times a positive skin is noted, but the same

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test on control patients without arthritis often reveals a similar reaction. Protein sensitivity tests are carried out. Complete examinations of the blood are done as is a stool examination, including reaction and the evidences of carbohydrate or other food intolerances. The functional time of the gastro-intestinal tract is determined. Other investigations of the gastro-intestinal tract are carried out as indicated. In other words, every attempt is made to locate possible etiological factors, but in so doing, the condition of the joints is not ignored.

Frequently there is a history of bad feeding and precociousness about certain kinds of foods, too much starch, and a history of constipation and occasionally diarrhea. Possible foci of infection are frequently found but the removal of such foci has been usually disappointing.



Fig. 1. Child on a Bradford frame, with his lower extremities in counterpoised traction which allows active motion of all joints. The upper extremities may be placed in a similar apparatus.

THErapy—GENERAL MEASURES

Ordinarily, the child is placed upon a low carbohydrate diet with emphasis given to the essential food elements, particularly vitamins B, D, and A. Iron is given if there is evidence of hypochromatic anemia which is usual. The amount of food given depends upon the nutritional state of the individual; usually it is poor, so that a high rather than a low caloric diet is given. Whatever other value this regime has, the appetites are better, the nutrition of the patients improve, their bowel function is more satisfactory and, empirically, there seems to be an improvement in their joints.

We attempt to give a reasonable exposure to sunlight and during the the winter months, if it is convenient, quartz light may be used.

Just as we have been disappointed in the removal of foci of infection, so have we been disappointed in the use of vaccines. We do believe that definite foci of infection should be removed, for even if there is no direct relationship, their removal should at least improve the general health of the child.

LOCAL MEASURES—THE CARE OF THE JOINTS

In the present state of our knowledge regarding arthritis of children, it is our feeling that the local care of the joints is at least 60 per cent of the therapy, provided the child is on a general regime which is satisfactory for a normal child.

The first principle in the care of the joints is rest. Trauma to the joints must be avoided. If weight-bearing joints are involved all weight bearing must be strictly prohibited. Rest for a long period of time is

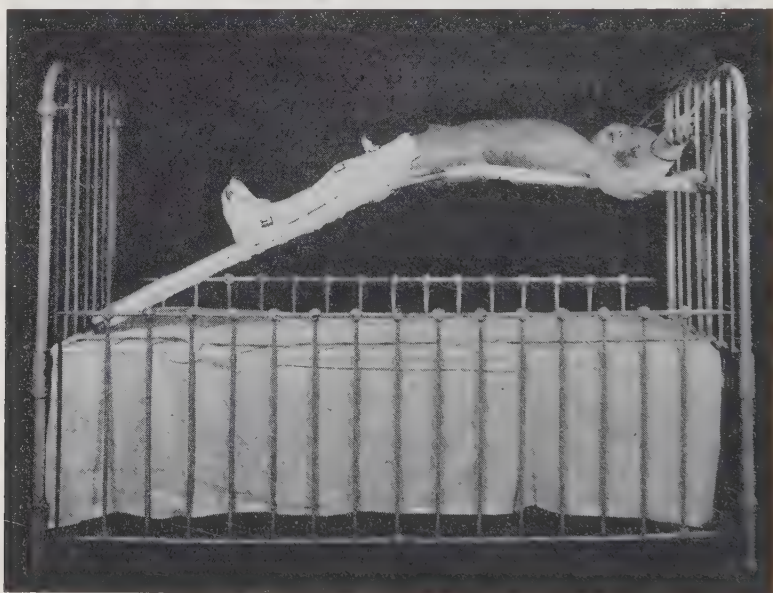


Fig. 2. Ready for the night. Child on hyper-extended Bradford frame with his extremities held in the corrected position by bivalved plaster casts. These are used at home during his sleeping and rest periods only; the remainder of the time he is out of apparatus.

more easily attained than in an adult, because of the simplicity of management and control and for economic reasons. Rest is of both general and local value.

However, if a child with the painful joints of an active arthritis is placed in bed and left there, the extremities develop progressive deformities and little motion is carried out in the parts which are guarded by continuous muscle spasm. There is extensive atrophy in the muscles, the bones and the joint cartilages. Even in normal joints, the cartilages become atrophic if they are immobilized for an extremely long period and there may be permanent damage. This damage is increased in the arthritic joints by the disease itself and muscle spasm.

With these considerations in mind, it has been our habit to place the involved joints in counterpoised traction. Ordinarily, we make use of the Thomas splint with the Pierson attachment both for the upper and lower extremities. These are counterpoised so as to allow motion in all directions (fig. 1). The patient is on a Bradford frame, which mitigates back deformities. If there is deformity present, the traction follows the line of deformity. The patient becomes comfortable, the muscle spasm decreases, and active motion of the involved joints is promoted in the apparatus. The apparatus facilitates this, both by decreasing muscle spasm and by allowing active motion of the part with less effort. During rest periods and at night, the splints may be locked in a position of maximal painless correction. Exercise in the apparatus is so carried out that the development of those muscles which combat the deformity is promoted. Baking and massage may be given at this time.



Fig. 3. Child of six years on admission November 12, 1932, two and one half years after the onset of typical Still's disease, showing the swollen joints, marked deformities, extreme muscle atrophy and general malnutrition. The little motion remaining in the joints was excruciatingly painful.

When the activity of the process has decreased enough so that he may be handled, the child is placed in the Hubbard tub for a few minutes at a temperature of 103 degrees Fahrenheit, following which, he is given supervised exercises in a pool or Hubbard tub in which the water is about 96 degrees Fahrenheit. The same types of exercises are given as might be given a patient with infantile paralysis to develop the atrophied muscles, but more emphasis is given to the development of an increased range of motion of the involved joints. Guided exercises are given but frankly manipulative procedures should never be adopted.

The child spends the greater part of the time during this period in the counterpoised apparatus, but as he improves, the time is gradually decreased.

If this regime were followed throughout the course of the disease, the cost would become excessive. It is continued until the deformities have been largely corrected and the activity has subsided. The child is then discharged from the hospital.

HOME CARE

Before the child is discharged home, a member of the family is carefully and thoroughly instructed as to the exercises, the diet and general regimen to be followed. Plaster casts, bivalved, are made to hold the ex-



Fig. 4. Three views of the same patient as in figure 3, eighteen months later, showing correction of his deformities and giving some idea of the motion in his joints. Weight-bearing is not yet allowed although he rides a tricycle freely.

tremities in the corrected position at night and at such other periods as are thought desirable (fig. 2). Frequently a Bradford frame is given on which the child sleeps.

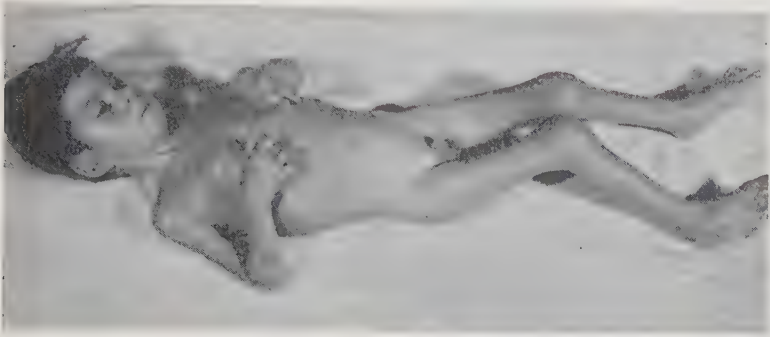


Fig. 5. Child of four years on admission January 1932, two and one half years after the onset of Still's disease. This picture is very similar to figure 3.



a

Fig. 6. a and b. Same child as that illustrated in figure 5, two years later, in braces. He is now walking with only one brace. Excellent motion of his joints is suggested.

It is at this point in the disease that the care of these cases has been unsatisfactory. The follow-up in the outpatient department has been inadequate.



b

the disease has largely subsided, usually with braces at the start. The best way to start walking is in the pool. Exercises are continued for a longer period of time than would ordinarily be thought necessary (figs. 5 and 6).

GENERAL RESULTS

The disease usually becomes arrested and if the joints are properly cared for during the acute stage, one may consider, in an intelligent, educated individual, a very hopeful prognosis for at least an economic independence.

In light of this experience, we have recently organized at the Children's Hospital, an arthritic clinic, the personnel of which consists of, in addition to an orthopedist, a pediatrician and bacteriologist, a physiotherapist, and a dietitian. The presence of both a pediatrician and an orthopedist gives a balanced attitude toward the patients and the study of the disease. The dietitian takes up with the parent, the dietary problems which arise in the care at home. The function of the physiotherapist is chiefly to instruct the patient and the parent, for we believe that the most effective physiotherapy is active exercise carried out frequently which, unless the economic status permits the employment of a physiotherapist in the home for a considerable period each day, can be done only by the parent or someone living with the patient. If prolonged adequate instruction is given, the average mother can carry these measures out effectively.

The patients are seen in the clinic often enough that adequate instructions may be given and they may be accurately followed (figs. 3 and 4).

We take the attitude of making haste slowly. Early walking is not a first consideration in these patients.

We allow weight-bearing only when

DISCUSSION

DR. ROBERT B. OSGOOD, Boston: Dr. Ober's and Dr. Green's paper and moving pictures speak for themselves. Prevention of deformity is of supreme importance. This means not just the routine use of physical therapy but the use of measures specially designed and persistently carried out not only to prevent deformity but also to retain and increase joint mobility and improve joint circulation. This is not, I am sorry to say, what physical therapy means to the average physician. Physical therapy is one of our most effective weapons against eventual restriction of function in the atrophic type. Of course this presupposes that the generalized disease is being attacked by all other weapons, such as rest, fresh air, sunlight, diet and the removal of sources of infection

NOTE: This paper has concerned itself primarily with the larger problem of the generalized atrophic arthritis of children. Arthritis in which a single or only a few joints are involved is treated with the same fundamental considerations, modified to suit the individual case. Cases of this latter type are, of course, a much simpler problem than Still's disease.

GOUT: CHANGES IN SYMPTOMS AND PURIN METABOLISM PRODUCED BY HIGH FAT DIETS IN FOUR GOUTY PATIENTS*

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It has been known for many years that there is some relationship between gout and uric acid, and many investigations of the uric acid metabolism of gouty patients have been carried out.¹ Because the number of cases of gout reported throughout the country is increasing, such studies are of especial interest at the present time. Some of the recent studies have shown that the methods of diagnosing the disease are apparently not wholly satisfactory, for in 100 cases an average period of fifteen years elapsed between the first appearance of symptoms and the establishment of the correct diagnosis.² The differentiation of gout from chronic arthritis when joints other than the big toes are involved seems to be particularly difficult. The authors feel that the experiments reported here may serve as a basis of a useful test in helping to establish a correct diagnosis.

A number of workers have found that there is an increase in the blood uric acid and a decrease in the amount of that compound in the urine when normal subjects fast or ingest diets high in fat. In 1924, as the result of long and careful study, Lennox described such findings during 22 fasting periods, each at least 8 days long, in 2 normal subjects and 22 patients with epilepsy.^{3, 4} When diets high in fat were fed at the end of these fasts no changes in the blood uric acid were observed, but when diets high in protein or carbohydrate were used there was a prompt return to the pre-starvation level in the blood within 24 or 48 hours. As the blood uric acid fell there was an increase in the amount of uric acid in the urine. Hoeffel and Moriarty, in 1924, noted an increase in the blood uric acid of two fasting children.⁵ Harding and his co-workers, in 1925, produced a marked increase in the blood uric acid concentration by giving high fat diets to women in the various stages of pregnancy.⁶ In these experiments a prompt return to normal values occurred as soon as high carbohydrate or high protein diets were fed.

It seemed logical to determine the effect of similar diets in gout, and therefore diets high in fat were fed to four gouty patients who came under our observation. The studies were carried out on the First Medical Service of the Buffalo General Hospital. To Dr. Nelson G. Russell, the attending physician, we are greatly indebted for advice and encouragement extended during the experiments. The diagnoses were made according to the criteria of Hench. The details of the diets were arranged by the dietitians of the hospital, based on McLester's tables.⁷ The purin content

*From The Buffalo General Hospital and The University of Buffalo School of Medicine.

of each diet was approximately equivalent to 0.042 gm. of uric acid per day, and the other constituents were varied to suit the needs of the individual patients and the experimental conditions which we wish to produce. The urinary uric acid was determined by the method of Benedict and Franke, and the blood uric acid by Folin's direct uric acid method.⁹

Much to our surprise striking changes in symptoms occurred when these diets were ingested. The clinical findings, which formed the most interesting part of the study, are described in the protocols of the separate experiments.

Case 1.—History[†]: E. H., a male, aged 52 years, was first seen in July 1930, when he entered the hospital for treatment of persistent headaches. During his stay he had an attack of gout in the left knee, characterized by increased warmth, pain and swelling, which lasted for about one week. Further questioning at this time revealed the fact that he had had periodic attacks of gout during the preceding 18 years, and that each of these incapacitated him for a period of from one to two weeks. During the intervals between the attacks he was completely free from joint symptoms. The joints most frequently involved were those of the knee and big toe. On two occasions tophi containing sodium urate crystals had been removed from the lobe of his right ear. In July 1932 many of the joints of the body were involved. There was marked swelling of the joints of the hands and feet. Both knees were swollen, warm and painful. It was necessary to give large doses of salicylates and opiates to control the pain. Small doses of colchicum did not help; large doses had not been tried.

Physical examination.—The patient was well nourished and well developed. The afternoon temperature was 101° F. and the pulse 110 per minute. He appeared to be suffering intense pain. The pharynx was red-dened and a few cervical lymph nodes were enlarged. No râles were heard in the lungs and the breath sounds were not changed. The left border of the heart was 11 cm. from the mid-sternal line in the sixth interspace. The aortic second sound was accentuated. No murmurs were heard. The blood pressure was 175 mm. of mercury systolic and 100 mm. diastolic. The liver was not tender but the edge was palpable. No masses were felt in the abdomen. The hands, wrists, knees, and ankles were swollen, warm, tender on pressure, and very painful on motion.

Laboratory examinations.—The urine was cloudy, with a specific gravity ranging from 1.010 to 1.020. The albumin content was 2+. The sediment contained 30 to 40 white blood cells per high power field. The phenolsulphonphthalein excretion was 40 per cent in two hours. There was 80 per cent of hemoglobin present (Talquist). The red cell count was 4,800,000, and the white count 9,300, with 63 per cent polymorphonuclear cells. The blood Wassermann reaction was negative. The blood uric acid was 6, the urea nitrogen 14, and the glucose 130 mg. per 100 c.c.

X-ray examination.—The distal ends of the first phalangeal joints of the great toes had a punched out appearance which suggested gout.

[†]A preliminary report of the results obtained upon this patient was given in the Proceedings of the Buffalo Academy of Medicine.¹⁰

Course.—At a time when the patient had been practically free from symptoms for two weeks he was put on a high fat diet consisting of 50 grams of carbohydrate, 50 grams of protein, and 220 grams of fat. When he had been on this diet 7 days pain, swelling and tenderness developed in the joints of his feet and ankles. During this period the blood uric acid increased. The initial value was 5.5 mg. per 100 c.c., and after 11 days on the diet it reached 8 mg. per 100 c. There was also during this period of a diminution of the amount of uric acid in the urine.[†] No medication of any kind was given, but the diet was changed to one consisting of 380 grams of carbohydrate, 60 of protein, and 130 of fat. Within two days a marked improvement in the symptoms took place. The carbohydrate was then reduced to 200 grams because the patient could not eat the larger amount. Pain did not return, but the blood uric acid remained high for 14 days. After that period of time 250 grams of liver were fed. This did not cause an exacerbation of symptoms or a significant further increase in the blood uric acid. The blood uric acid remained high (between 7.2 and 7.8 mg. per 100 c.c.) for the next 11 days. Five days later, just before the patient left the hospital, it fell to 5.7 mg., the value found before the dietary experiments were begun. Throughout this 25 day period the basal diet was 200 grams of carbohydrate, 60 grams of protein, and 130 grams of fat.

The patient has been seen every two or three weeks in the Out Patient Department up to the present time (October, 1934). He has had a few twinges of pain in the small joints of his hands and feet which have lasted for two or three hours at a time. His general health has been good.

Case 2.—*History.*—W. R., a man, was seen for the first time in February, 1934. He had been well until January, 1930, when he had an excruciating pain in the left ankle. This disappeared in a few days, but shortly afterwards the right knee became swollen and very painful. A diagnosis of rheumatism was made in another hospital, and his tonsils were removed one month later.

Each year after that time he had several attacks, presumably of gout, which involved the weight-bearing joints. One of these, in 1932, also involved the small joints of the hands. He found that strenuous exercise, an alcoholic debauch, or thorough chilling provoked attacks. Each episode followed the same course. There was marked swelling, pain, tenderness and limitation of motion. Within 10 to 14 days there was complete recovery from joints symptoms.

Albuminuria was found in 1926. A molar tooth was extracted and an antum washed in 1933 without producing a flare-up of symptoms.

Physical examination.—The patient was fairly well nourished. His temperature was 99.6° F. No tophus was found. The heart was slightly enlarged. No heart murmurs were heard. The blood pressure was 130

[†]Marked temporary fluctuations in the rate of excretion of uric acid are common in gouty patients,¹¹ and were found during our experiments. These made interpretation of the urine findings difficult, for it was necessary to follow the general trend of changes in values, and to ignore occasional large variations in them. The interpretation was further complicated by failure to collect accurate 24 hour specimens in all instances. To minimize the effect of such failures the creatinine content of each urine was determined, the ratio between creatinine and uric acid calculated, and variations in the values of this ratio studied.

systolic and 80 diastolic. Several joints were involved. Those showing the most pronounced symptoms were the left knee and ankle. There was marked swelling, tenderness, and limitation of motion. No urethral discharge was present.

Laboratory examination.—Analyses of the urine showed that the specific gravity varied between 1.013 and 1.020, and that it contained 3+ albumin and a few hyaline casts. The hemoglobin was 68 per cent (Sahli). The red blood cells numbered 4,400,000, and the white cells 14,000, with 75 per cent polymorphonuclear cells. The blood sedimentation rate was greatly increased. The uric acid concentration was 6.2, and the urea nitrogen 35, the nonprotein nitrogen 71, and the creatinine 2 mg. per 100 c.c. of blood.

Course.—He recovered from his joint symptoms in a few days, and stated that, judging from his past experiences, he would not have another attack for some months. After one week he consented to ingest a diet containing 60 grams of carbohydrate, 60 grams of protein, and 230 grams of fat. Within three days he felt poorly. The left hand and knee were swollen and painful. The joints in the left hand were especially sore. He felt so ill that he stayed in bed, although previously he had been ambulatory for five days. No medication of any kind was given, and the diet was changed to one consisting of 400 grams of carbohydrate, 70 grams of protein, and 60 grams of fat. There was marked improvement in his symptoms within 48 hours. No significant variations in the blood uric acid were found at any time during the experiment. In three determinations on different days the values lay between 5.5 and 5.8 mg. per 100 c.c. of blood. The explanation of this constancy of the blood uric acid seems obvious. The diet high in fat was taken for only three days, and demonstrable changes probably should not have been expected.

During the five months which have elapsed since the experiment there has been no recurrence of joint symptoms.

Case 3.—History. A. A., a white Jewish male, aged 74 years, was admitted to the First Medical Service in October, 1933. During the preceding 23 years he had had at least 12 attacks of gout. Each time there was pain, redness, and swelling of the joints of the lower extremities, particularly of the big toe joints, the right knee and the right ankle. Between attacks he felt entirely well. Two weeks before he entered the hospital pain developed in the right foot. This was followed a day later by swelling of the subcutaneous tissue. During this period he felt poorly.

For ten years dyspnea on exercise and occasional edema of the ankles had been present. He had had nocturia for three or four years, and had lost 30 pounds during the two years preceding admission.

Physical examination.—He seemed a well-nourished male. No tophus was seen. The area of precordial dulness was slightly enlarged. No murmurs were heard on auscultation of the heart. The blood pressure was 128 systolic and 90 diastolic. The liver edge was palpable. The right foot was warm, painful to the touch, and could be moved very little without causing great pain. No other joints were involved.

Laboratory examination.—The specific gravity of the urine varied from 1.015 to 1.018 in various specimens, and 3+ albumin was present. The hemoglobin was 78 per cent (Sahli), and the red cells numbered 4,200,000. There were 12,000 white cells; 75 per cent of these were polymorphonuclear cells. The blood Wassermann was negative. The basal metabolic rate was minus 3 per cent. The concentration of uric acid was 6.8, of urea nitrogen 34, and of glucose 130 mg. per 100 c.c. of blood.

X-ray examinations.—The feet showed a decreased density in the distal ends of the first metatarsal bones and two small areas which had a punched out appearance.

Course.—He entered the hospital approximately at the end of an attack of gout. After he had been without signs or symptoms for one week he predicted that, judging from past experiences, he would not have another exacerbation for at least 10 months. A diet of 20 grams of carbohydrate, 30 grams of protein, and 300 grams of fat was then given. Within 48 hours pain developed in the right foot. Shortly afterward it became swollen and tender. No medication was given, but the diet was changed to one consisting of 350 grams of carbohydrate, 60 grams of protein, and 8 grams of fat. Within 72 hours all the signs and symptoms had disappeared. After he had been free from pain for one week he agreed to take the high fat diet again. Within two days he noticed the same symptoms and signs which he had felt during the previous test. The diet was changed to 440 grams of carbohydrate, 80 grams of protein, and 120 grams of fat, and his symptoms disappeared within three days. At no time during the experiment were significant changes in the blood uric acid found. Seven of eight determinations gave values between 6.5 and 7.0 mg. per 100 c.c., and the eighth was only slightly lower than the others—5.8 mg. This lowest value was present on the second day of the second period on a high fat diet.

The patient left the hospital 13 days after the last bout had subsided. He was seen two months later in the Out Patient Department, and reported that he had been free from symptoms during the intervening period.

Case 4. History:—N. G., a white male, aged 16 years, was admitted to the First Medical Service on February 22, 1934. He stated that in 1932, following a respiratory infection, hematuria, albuminuria, edema of the face and legs, and an increase in blood pressure had developed. It was noticed that tophi were present in the lobes of his ears at that time. The family physician advised the boy to be very moderate in exercising and to eat very little meat. He had rarely tasted liver and other internal organs. He had never used alcohol. During the latter part of December, 1933, he suffered his first joint pains, which began in the right ankle. It was red, swollen, and very painful. He could not allow the bed clothes to touch his foot. The attack lasted 10 days and was followed by complete recovery. He was well for 5 weeks, and then the left wrist became swollen, tender, and painful for one week. Following this there was no residual deformity or loss of function. He entered the hospital at the end of his third attack, which had begun one month after the previous one. This time the

left ankle and big toe joint were involved. There was some pain and tenderness with limitation of motion.

His father and four males on his father's side had died of kidney trouble. No family history of gout was obtained.

Physical examination:—He was a well-nourished male and not acutely ill. Tophi were present in both pinnae. The pharynx was reddened. The heart sounds were regular, but the first sound at the mitral area was roughened, and the P_2 was greater than the A_2 . The blood pressure was 142 systolic and 100 diastolic. The left knee was red and swollen. It was warm and extremely painful when touched. There was no evidence that other joints were actively involved, or that they had been affected by his previous bouts.

Laboratory examinations:—The specific gravity of the urine varied from 1.007 to 1.022, and no albumin or glucose was found. The hemoglobin was 90 per cent (Sahli). The red blood cells numbered 4,250,000 and the white cells 9,050, with 67 per cent polymorphonuclear cells. The two hour urine concentration test showed a variation in specific gravity from 1.003 to 1.015. The night out-put of urine was about one third of the day out-put. The blood sedimentation rate was greatly increased when he was admitted and normal when he was discharged. The basal metabolic rate varied with therapy from minus 29 per cent to plus 3 per cent. No agglutinins for *Streptococcus hemolyticus* (AB13) were found in the blood serum. The blood chemical findings on admission were: glucose 143, calcium 11.9, inorganic phosphorus 4.4, cholesterol 153, uric acid 7.6 mg. per 100 c.c. of blood.

X-ray examination:—The feet and left wrist did not reveal punched out areas or signs of decalcification. No renal or bladder calculi were seen.

Course:—With few signs of the active attack remaining he was placed on a diet of 225 grams of carbohydrate, 60 grams of protein, and 70 grams of fat. Sodium salicylate and colchicine were given for one day. He felt better for a few days, but then several joints became involved. After six days the symptoms disappeared and he felt very well. During this period he was taking 2 mg. of colchicine daily.

After he had been clinically free of symptoms for one week the diet was changed to 50 grams of carbohydrate, 50 grams of protein, and 250 grams of fat. The colchicine, 2 mg. daily, was continued for one week of this experimental period. The amount of fat was raised to 300 grams, and six days later he had pain in his wrists and metacarpal joints. There was no swelling at this time. On the following day the pain increased and he felt poorly. The third day after the onset of the attack pain appeared in the right shoulder, and after another 24 hours there was swelling in the left wrist and hand. Then the joints of the right hand became involved, and within another day the joints of the left foot were sore. The pain persisted in all of the joints which had already been affected. An injection of 50 c. c. of 50 per cent glucose intravenously gave a little relief, but this lasted only for an hour. The pain now was almost unbearable when one touched the bed. The diet was changed to one consisting of 350 grams of carbohy-

drate, 50 grams of protein, and 50 grams of fat. Within two days he felt very much better, although no medication of any kind was given.

During the time he was on the high fat diet the concentration of uric acid in the blood increased from a value of 8.6 to one of 16.0 mg. per 100 c. c., and there was a significant decrease in the rate at which uric acid was excreted in the urine.¹ There was no drop in the level of uric acid in the blood during the first eight days when he was taking the high carbohydrate diet. Determination on four occasions gave values between 13.5 and 15.0 mg. per 100 c.c. Again it should be pointed out that the patient was free from symptoms during this period. Because of the persistent hyperuricemia he was given sodium salicylate in doses of 2 grams every two hours. The blood uric acid dropped to 10 mg. per 100 c.c. after this drug had been used for three days, and eight days later, with continuation of the therapy, it reached 6.5 mg.—a value slightly lower than the one found on admission.

Five days after the conclusion of the experiment just described, while the patient was still on a diet low in fat (50 grams) and high in carbohydrate (350 grams) there was a recurrence of symptoms which lasted for five days. At this time the basal metabolic rate was minus 29 per cent. Thyroid extract (Parke Davis and Co.) was given in doses of 0.03 grams three times a day to raise the basal metabolism and to aid in the excretion of uric acid. No other medication was used. During the remainder of his stay in the hospital he was free from symptoms except for occasional fleeting pains in the hands. Ingestion of 500 grams of liver did not aggravate his condition. The diet was kept at 500 grams of carbohydrate, 50 grams of protein, and 50 grams of fat.

During three months of observation in the Out Patient Department he has had only two or three days of mild pain.

DISCUSSION

The ingestion of high fat diets by these patients with gout resulted in certain metabolic and clinical changes which merit detailed discussion. The metabolic findings will be discussed first. Two of the patients took the diets high in fat for fairly long periods. In the blood of each of them the amount of uric acid at the end of the experiment was markedly higher than it had been at first. Patient number 1 showed a uric acid concentration of 8 mg. per 100 c.c. after he had been on the diet for eight days. This value was 60 per cent higher than the one found when he first presented himself at the clinic. Patient number 4 took the diet for 11 days. On the last day of the test 16 mg. of uric acid was present in each 100 c.c. of his blood. This was double the concentration present at the beginning of the test. Two other patients developed such extreme pain when they took the diet that it was necessary to discontinue the diet after three days. Neither of them showed any significant change in the blood uric acid. The results closely resemble those found in various investigations of persons not suffering from gout; high fat diets fed for a week or more regularly cause increases in the blood uric acid comparable to those observed in the experiments first described, while similar diets fed for shorter periods do

not cause such changes. Patients with gout and normal subjects therefore show the same metabolic response to diets high in fat.

When, however, attention is centered upon the rate at which the blood uric acid values decreased after the diets high in fat were replaced by those high in carbohydrate, a striking difference between patients with gout and those with other conditions is seen. In all previous articles dealing with such metabolic studies in non-gouty subjects it has been stated that the blood uric acid returned promptly to normal when the high fat diets were discontinued. Neither of our subjects who ingested the diet for a long period showed a prompt change of this kind after the diet had been stopped. It was not until a diet high in carbohydrate had been fed to patient number 1 for twenty-four days that the blood uric acid fell to the level present before the high fat diet was begun, and such high values were still present eight days after the diet of patient number 4 had been changed that we felt it desirable to use salicylates to hasten the excretion of uric acid. There seems to the authors to be some resemblance between this marked persistence of increased blood uric acid values after the ingestion of high fat diets and the delay in the excretion of uric acid after feeding diets rich in purins,¹² or after injecting uric acid,¹³ which patients with gout regularly show. It seems probable that all three findings result from the same underlying cause.

The most interesting observations in this study were the changes in the clinical symptoms of the patients. There was an exacerbation of the signs and symptoms when these patients were fed diets high in fat, and in a majority of the experiments the attacks developed within a few days after they had been placed on the diet. It should be stated explicitly that these clinical findings were fairly independent of changes in the uric acid content of the blood, for (1) they were noticed in experiments which were too short in duration to cause variations in the blood uric acid, and (2) in two cases with marked increases in the blood uric acid the symptoms decreased or disappeared while the blood uric acid was still high. These changes in symptoms might have been due to changes in the amount of uric acid in the tissue around the joints, but no evidence is available to prove such a theory.

The regularity with which this clinical response was observed led us to investigate the relationship between the ingestion of high fat diets and the occurrence of joint symptoms in other conditions. No mention of the development of such symptoms is contained in the physiological papers to which reference has already been made. Wright and Hubbard,¹⁴ who fed diets high in fat to 15 patients with chronic arthritis, did not encounter any noticeable exacerbations of the signs of the disease.¹⁵ The results of a few experiments of our own were similar to those of the authors just mentioned. Four patients with chronic arthritis were fed diets high in fat for at least seven days, and there was no change in the clinical manifestations of the disease in any instance.

Since patients with gout appear regularly to experience an exacerbation of joint symptoms when they are fed diets high in fat, and since other groups of patients do not do so, the authors wish to propose the follow-

ing test for differentiating gout from various forms of chronic arthritis. Feed a diet consisting of 250 to 350 grams of fat, 50 grams of protein, and 30 to 50 grams of carbohydrate for a period of five to seven days. If within that time pain in the joints has developed, or if existing mild joint pains have markedly increased in severity, a diagnosis of gout must be carefully considered. The symptoms which may develop can be promptly relieved by feeding a diet high in carbohydrate and low in fat.

SUMMARY AND CONCLUSIONS

When diets high in fat, and low in carbohydrate and protein, were fed to patients with gout the following effects were observed:

(1) The concentration of uric acid in the blood increased and the amount excreted in the urine decreased if the diets were ingested for reasonably long periods. These results were approximately the same as those which have been found in the study of normal subjects.

(2) When diets high in fat were withdrawn and replaced by diets low in fat and high in carbohydrate the blood uric acid returned very slowly to the initial level. This result differs from experience with normal subjects, who under similar conditions show a prompt return of the uric acid in the blood to normal values.

(3) Each time a patient was given a diet very high in fat an attack of gout occurred within a few days. The joint symptoms subsided shortly after the patients were placed on a low fat—high carbohydrate diet.

(4) These variations in the clinical symptoms were not directly dependent upon changes in the uric acid concentration in the blood. Attacks were noted before increases in the blood uric acid occurred in some instances, and disappeared while the blood uric acid was still high in others.

(5) Similar diets did not cause exacerbations in the symptoms of patients suffering from chronic arthritis.

The authors feel justified in making the following recommendations as the result of these experiments:

(A) The development of exacerbation of joint symptoms following the ingestion of a diet high in fat and low in carbohydrate and protein for several days may serve as a useful test in the differential diagnosis of gout.

(B) Diets high in fat and low in carbohydrate should be avoided in the treatment of patients with gout.

DISCUSSION

DR. PHILIP S. HENCH, Rochester, Minnesota: A few years ago I reported on a study of 100 cases of gout. An outstanding fact was that it took about 1500 years to diagnose these 100 cases, that is, an average of 15 years elapsed between the first attack and the establishment of the correct diagnosis. The reason for such delay lies in the erroneous idea that the characteristic changes used in the past for diagnosis are expected to appear reasonably early and that hyperuricemia, punched-out areas, and preferably tophi should be present before a diagnosis is made. Palpable or roentgenographic tophi are generally late phenomena and even the blood uric acid may be normal for some time after the onset of gout. We obviously need more help in making early diagnosis.

Even when the physician is certain of the diagnosis a patient often refuses prolonged dietary restrictions unless he can be shown certain foods are harmful. Herein lies one of the values of provocative tests in gout, but these test diets in use today are generally of doubtful value. When the response to a high purin test is undoubtedly positive, its significance is appreciated, but unfortunately the responses are often unconvincing even in known gout. Less than half of a series of our patients with known gout noted sig-

nificant increases in symptoms and in some the blood uric acid was lower just after than before the test diet. In about 15 per cent of a series of cases of undoubted chronic atrophic arthritis increases of pain were noted on the test diet, probably coincidental, however.

The report of Drs. Lockie and Hubbard is of particular interest because it proposes a more useful provocative test and suggests a definite therapeutic corollary as well as a new line of thought concerning the pathogenesis of gout. While Harding and his colleagues spoke of the effects of a "high fat diet" both they and Umeda insisted that "a diet sufficiently high in fat to produce ketosis" was necessary to produce hyperuricemia. The diets used by Lockie and Hubbard were probably not ketogenic as it is practically impossible to develop ketosis on a carbohydrate intake of over 15 to 20 grams. It must be determined whether ketosis is a requisite for a provocation. We have given a few patients with chronic atrophic arthritis, diets high in fat and with the carbohydrates varying between 15 and 50 grams. No flare-up of joint symptoms was noted and no unusual rise in blood uric acid was noted unless ketosis was established.

The therapeutic corollary is of greater interest and importance. It may be possible for a patient with gout to enjoy less purin restrictions if he is protected by a high carbohydrate intake. These studies indicate anew that gout is not a problem just of purins or uric acid but is more profound. The French have shown that cholesterol is precipitated in tophi in addition to urates. This work might be interpreted as indicating in gout a disturbance of fat as well as purin metabolism. To date, however, it is thought that fats merely lower the kidneys' ability to excrete urates. In the meantime with the increasing use of ketogenic diets for urinary tract infections, if a patient being so treated suddenly develops acute arthritis, an investigation for gout seems in order.

DR. FRANCIS C. HALL, Boston: This paper is important for several reasons. It calls attention to the fact that gout still exists in the United States. Erroneously calling it rheumatic fever, toxic, traumatic or hypertrophic arthritis, we are misdiagnosing a large number of cases of typical and atypical gout because we fail to think of it.

It is important because it suggests a more accurate method of diagnosis. There are many cases of arthritis without tophi with or without the typical series of attacks, but with borderline concentrations of blood uric acid, and whose roentgenograms may reveal punched out areas in bones in which it is difficult to make a diagnosis. A provocative diet high in purins is of value in some cases, but a high fat diet may prove of greater diagnostic merit. This study emphasizes what has been previously known but not generally recalled that a high fat intake retards urate elimination by kidneys and that the diet in gout should be high in carbohydrates and not only low in purines but also in fat. We must also not forget what Folin, Berglund and Derick demonstrated—that a high protein diet stimulates urate excretion.

There are many unsolved problems concerning gout and uric acid: Why does not gout attack patients with a high blood uric acid such as in nephritis, leukemia, polycythemia, and pneumonia? What part, if any, does the liver play and why is there a diminution in the excretion of uric acid before an attack? Searching for other leads in solving these problems we have found a low metabolic rate in some of our patients between their attacks of gouty arthritis. They have also exhibited stigmata, a history, and a response to thyroid suggestive of thyroid deficiency. If this is not a coincidental finding it may indicate that slow blood flow may be a conditioning factor. Burian showed that exercises increased the excretion of uric acid 3-5 times. Trauma will precipitate gout and we have seen several patients whose pronated feet lead to trauma of knees and toes. Correction of such defects may be important.

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